

The Effect of Zoledronic Acid on Bone Mineral Density in Patients Undergoing Androgen Deprivation Therapy

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Abstract

Purpose: The aim of this study was to evaluate the efficacy and safety of zoledronic acid compared with placebo in preventing bone mineral density (BMD) loss and suppressing bone markers when initiated during the first year of androgen deprivation therapy in patients with locally advanced prostate cancer. **Patients and Methods:** Patients were randomized to receive zoledronic acid 4 mg or placebo intravenously every 3 months. Lumbar spine (LS) and total hip BMD was measured using dual-energy x-ray absorptiometry at baseline and at week 52. N-telopeptide (NTX) and bone-specific alkaline phosphatase (BSAP) were evaluated at baseline and every 12 weeks. Safety assessments were performed throughout the study. **Results:** Efficacy analyses included 106 patients and 109 patients in the zoledronic acid and placebo groups, respectively. At week 52, the least squares mean BMD percentage differences were 6.7% for LS and 3.7% for total hip ($P < 0.0001$ for both). In the zoledronic acid group, decreases in NTX (-14% to -28%) and BSAP (-31% to -37%) levels were significant and sustained; changes in NTX levels and LS BMD ($r = -0.25$; $P = 0.04$) and in BSAP levels and hip BMD ($r = -0.28$; $P = 0.02$) were significantly correlated. Only traumatic fractures were reported for 2 and 3 patients receiving zoledronic acid and placebo, respectively. One patient in each group experienced acute renal failure. Osteonecrosis of the jaw was not reported. **Conclusion:** Zoledronic acid (4 mg intravenously every 3 months) was safe and effective in preventing bone loss and reducing bone turnover in patients with prostate cancer when initiated during the first year of androgen deprivation therapy; patients with low baseline BMD experienced the greatest benefit.

Introduction

Androgen deprivation therapy (ADT), a mainstay of prostate cancer therapy, increases bone resorption, decreases bone mineral density (BMD) over time, and ultimately, increases the risk of fractures.¹⁻¹⁰ Bisphosphonates have been shown to safely and effectively prevent ADT-associated osteoporosis in patients with locally advanced prostate cancer.^{2,11} The results of 1 study showed that pamidronate prevented bone loss associated with ADT in patients with nonmetastatic prostate cancer; however, increases in BMD were minimal ($< 1\%$).² The results of another study showed zoledronic acid (4 mg intravenously [I.V.] every 3 months for 5 cycles) not only prevented BMD loss compared with placebo, but significantly increased lumbar spine (LS; 5.6%) and total hip (TH) BMD (1.1%) in patients with prostate cancer starting ADT.¹¹

When the current study was conceptualized, the benefit of initiating zoledronic acid during the first year of ADT, when most ADT-associated bone loss occurs, was unknown.¹⁰ Furthermore, the effects of zoledronic

acid on markers of bone turnover in this patient population had not been evaluated. Therefore, this study aimed to compare the effects of zoledronic acid (4 mg I.V. every 3 months) and placebo on bone loss and serum biomarkers of bone resorption (N-telopeptide [NTX]) and bone formation (bone-specific alkaline phosphatase [BSAP]) when initiated during the first year of ADT in patients with locally advanced prostate cancer.

Patients and Methods

Fifty-six US academic and community-based urology practices enrolled patients in this prospective, double-blind, randomized, placebo-controlled study. Patients with histologically confirmed, nonmetastatic prostate cancer within 1 year of starting ADT (luteinizing hormone-releasing hormone [LHRH] agonist with or without antiandrogen) for an intended duration of ≥ 12 months or who had received an orchiectomy within 2 weeks of study screening were eligible for study participation. All patients were required to have a T score of ≥ -2 in the LS (L₂-L₄) and TH, an Eastern Cooperative Oncology Group performance status of ≤ 2 , and a life expectancy of ≥ 12 months. Patients were excluded if they had received previous treatment for osteoporosis, bisphosphonate therapy or systemic corticosteroids within 12 months, or anabolic steroids/growth hormones within 6 months; were receiving diethylstilbestrol; had concomitant or previous malignancies or other comorbid conditions that could affect study completion; or had a history of lumbosacral spine surgery, bilateral hip replacement or surgery, abnormal renal function, or known hypersensitivity to any bisphosphonate. The institutional review boards of the participating sites approved the study design. Informed consent was obtained from patients before randomization.

Patients were randomized to receive zoledronic acid 4 mg or placebo administered I.V. over 15 minutes every 3 months for 48 weeks. The zoledronic acid dose and schedule in our study was selected, in part, based on the results of a study reported by Smith and colleagues,² which showed that ADT-induced bone loss stabilized in patients with prostate cancer receiving pamidronate I.V. every 3 months for 48 weeks. The investigators hypothesized that a similar schedule using the more potent bisphosphonate zoledronic acid (4 mg I.V. every 3 months) would not only stabilize but increase BMD in men with prostate cancer receiving ADT. Additionally, this dosing schedule was selected because it coincides with the every-3-month dosing schedule of the most common ADT regimens. In this study, patients were also instructed to take a daily calcium supplement (500 mg) and a multivitamin containing vitamin D (400-500 IU/L) for the duration of the study.

The primary endpoint of the study was percentage change in LS (L₂-L₄) BMD from baseline in patients receiving zoledronic acid compared with placebo. Secondary endpoints included change in TH BMD and serum NTX and BSAP levels.

Bone mineral density was measured using Hologic or Lunar dual-energy x-ray absorptiometry (DEXA) devices at baseline and at the final visit. All DEXA devices were standardized and cross-calibrated using 2 Bio-Imaging Bona Fide Phantoms.¹² T scores ($[\text{BMD} - \text{peak bone mass}]/\text{standard deviation} [\text{SD}]$)

were calculated based on manufacturer-specific reference values for peak bone mass and SD, which vary slightly depending on sex (GE Lunar and Hologic) and ethnicity (Hologic). A central reader analyzed all DEXA scans for the efficacy analysis. Serum NTX concentrations were measured using the Osteomark NTX assay, and serum BSAP levels were measured using the Tandem-R Ostase assay or the Access Ostase assay. Random, nonfasting blood samples were used to measure serum bone marker levels at baseline, at every 12 weeks, and at the final visit. A central laboratory analyzed all serum biochemical marker samples.

Adverse events (AEs) were assessed at every visit and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.¹³ Serum creatinine (SCr) levels were assessed at screening, before each infusion, and at the final visit. A significant increase in SCr level (≥ 0.5 -mg/dL increase from a baseline of < 1.4 mg/dL, ≥ 1 -mg/dL increase from a baseline of ≥ 1.4 mg/dL, or doubling of the baseline value) required study drug cessation until the SCr level returned to $\leq 10\%$ above the baseline level.

Based on a 2-sample *t* test (80% power, significance level of 0.05) to detect an expected 4% difference (9% SD) between treatment groups in LS BMD change from baseline (primary efficacy endpoint) and to allow for a dropout rate of 20%, a sample size of ≥ 100 patients in each treatment group was required.¹¹ All randomized patients who received ≥ 1 study drug infusion and underwent ≥ 1 postbaseline evaluation were included in the efficacy analysis. The safety analysis included all randomized patients who received ≥ 1 study drug infusion.

A 2-sample *t* test and Pearson χ^2 test were used to compare continuous and discrete demographic and baseline variables, respectively. For the primary and secondary endpoints, an analysis of covariance model was used to compare treatment groups and determine a 95% confidence interval (CI) for the adjusted mean difference between groups (zoledronic acid minus placebo). Differences between baseline and postbaseline variables within treatment groups were reported using summary statistics and percentage changes. Pearson correlation coefficients were used to evaluate the relationship between changes in LS or TH BMD and NTX or BSAP levels from baseline to week 52.

Results

Patient Demographics

Between April 21, 2003, and May 19, 2005, 222 patients were randomized to receive zoledronic acid ($n = 112$) or placebo ($n = 110$). Baseline characteristics were similar between the 2 groups (Table 1). The most common baseline osteoporosis-related risk factors, other than ADT and/or low testosterone level for both treatment groups, were older age and lack of vitamin D and/or dairy products as a child or adult. All patients had ≥ 1 osteoporotic risk factor at baseline, and 74% and 82% of patients receiving zoledronic acid and placebo, respectively, had ≥ 3 risk factors. One placebo-treated patient with a baseline T score < -2 was erroneously randomized. All randomized patients were included in the safety analysis; 106 (94.6%) zoledronic acid-treated patients and 109 (99.1%) placebo-treated patients were included in the efficacy analysis.

Table 1 Patient Demographics*

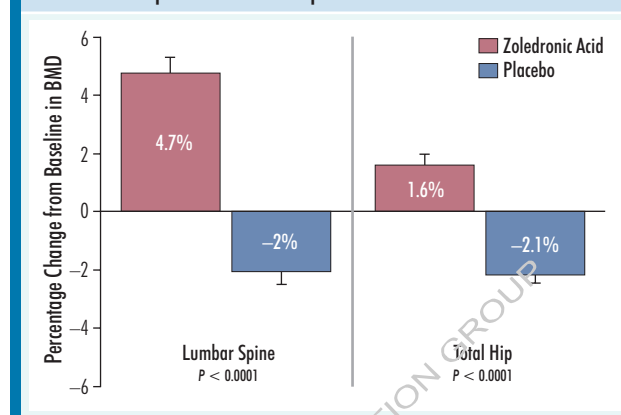
Demographic Variable	Number of Patients (%)	
	Zoledronic Acid	Placebo
Number of Patients Enrolled	112	110
Number of Patients in the Efficacy Population	106 (94.6)	109 (99.1)
Number of Patients in Safety Population	112 (100)	110 (100)
Median Age, Years (Range)	74 (44-88)	73 (47-89)
Ethnicity		
White	98 (87.5)	97 (88.2)
Black	8 (7.1)	9 (8.2)
Other	6 (5.4)	4 (3.6)
Type of ADT		
LHRH agonist with antiandrogen	46 (41.1)	35 (31.8)
LHRH agonist without antiandrogen	66 (58.9)	75 (68.2)
Orchiectomy	0	0
Osteoporosis Risk Factors		
ADT and/or low testosterone level	111 (99.1)	110 (100)
Adult broken bones	27 (24.1)	31 (28.2)
Aged ≥ 65 years	89 (79.5)	87 (79.1)
> 2 Alcoholic drinks per day	6 (5.4)	8 (7.3)
Body mass index < 20	1 (0.9)	1 (0.9)
Corticosteroid therapy	3 (2.7)	0
Family history of osteoporosis	9 (8)	9 (8.2)
Lack of mobility/exercise	23 (20.5)	19 (17.3)
Lack of vitamin D/dairy products as adult [†]	32 (28.6)	41 (37.3)
Lack of vitamin D/dairy products as child [†]	51 (45.5)	44 (44)
Mother with history of hip fracture	10 (8.9)	10 (9.1)
Poor/frail health	8 (7.1)	10 (9.1)
Smoking	19 (17)	28 (25.5)
Treatment history [‡]	21 (18.8)	17 (15.5)
≥ 1 Risk factor	112 (100)	110 (100)
≥ 3 Risk factors	83 (74.1)	90 (81.8)

*Based on all randomized patients.

[†]No daily vitamin supplement containing vitamin D and calcium, daily TUMS[®] use, or < 4 servings of dairy products daily.

[‡]History of treatment for hyperthyroidism, rheumatoid arthritis, endocrine disorder, seizure disorder, dementia, anorexia nervosa, and/or bulimia.

Thirty-five (31%) and 17 (16%) patients in the zoledronic acid and placebo groups, respectively, did not complete the study. Reasons for early discontinuation in the zoledronic acid and placebo groups included AEs (8, 6; respectively); consent withdrawals because of AEs or study-related concerns (7, 1); consent withdrawals unrelated to AEs (12, 6); protocol violations (2, 2); and other reasons (6, 2). Patients in the zoledronic acid and placebo groups received a mean (SD) of 4.1 (1.5) and 4.6 (1.1) infusions, respectively; 77 patients (69%) and 93 patients (85%), respectively, received all 5 doses.

Figure 1 Bone Mineral Density Increased in Lumbar Spine and Total Hip

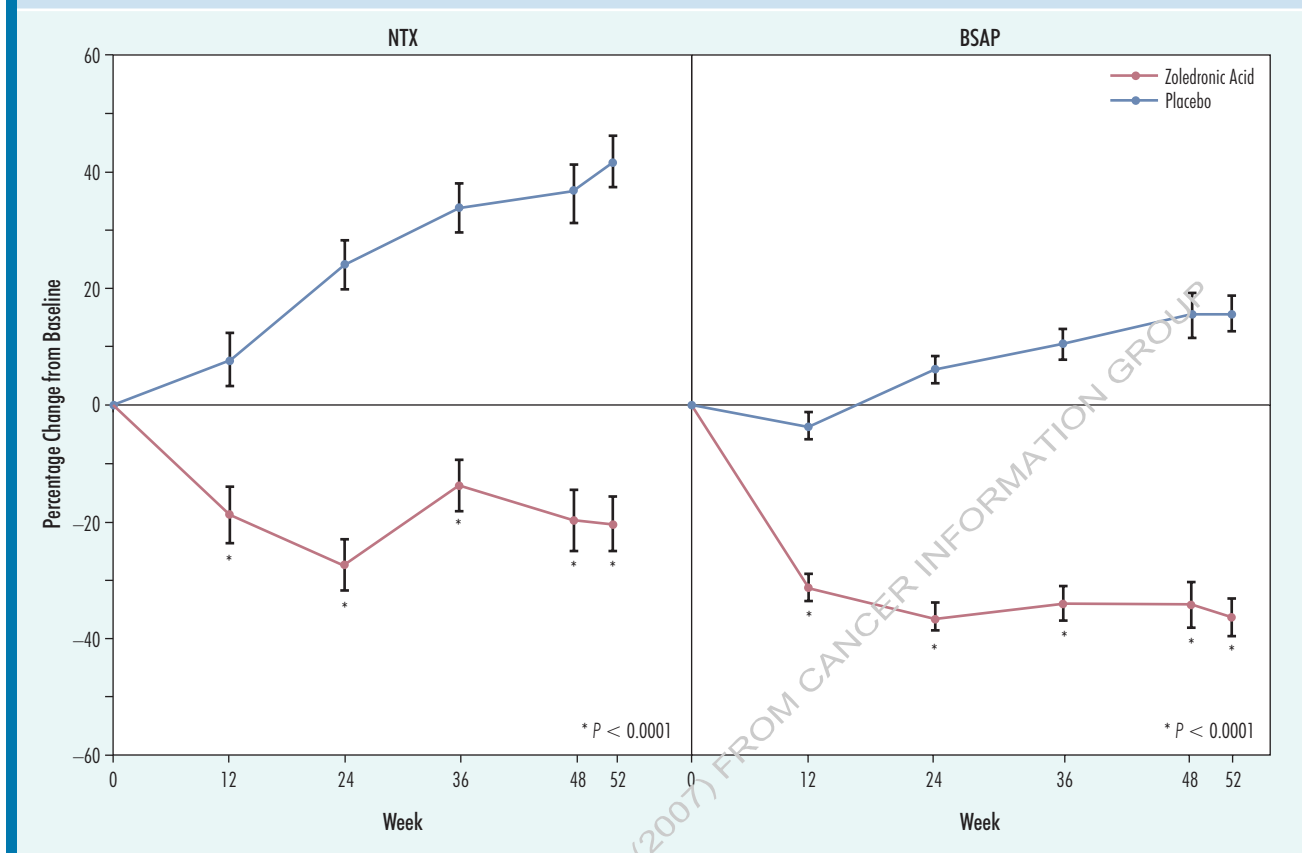
Least squares mean (standard error of the mean) percentage change from baseline in BMD of the LS and TH in men with locally advanced prostate cancer receiving androgen deprivation therapy and zoledronic acid or placebo. *P* values correspond to the difference in the percentage change between groups (zoledronic acid vs. placebo).

Bone Mineral Density

Lumbar spine and TH BMD measurements at week 52 were available for 76 patients (72%) receiving zoledronic acid; LS and TH BMD measurements were available for 91 (83%) and 93 (85%) patients, respectively, receiving placebo. Least squares mean values (adjusted for baseline and study center) with corresponding standard error (SE) of the means were used to assess the percentage change in BMD from baseline to study termination. Baseline BMD values were not evaluable for 2 zoledronic acid-treated patients and 1 placebo-treated patient. Bone mineral density increased significantly from baseline to week 52 in the zoledronic acid group in the LS (4.7%; SE, 0.49) and TH (1.6%; SE, 0.37; Figure 1). In patients receiving placebo, BMD of the LS (-2%; SE, 0.46) and TH (-2.1%; SE, 0.34) decreased significantly. At week 52, the differences between treatment groups in LS and TH BMD were 6.7% (SE, 0.65; 95% CI, 5.4-8; *P* < 0.0001) and 3.7% (SE, 0.49; 95% CI, 2.8-4.7; *P* < 0.0001), respectively. From baseline to study termination, LS BMD decreased by > 8% in 1 zoledronic acid-treated patient and 7 placebo-treated patients; a similar decrease in TH BMD was not observed in patients receiving zoledronic acid, whereas 3 patients receiving placebo experienced decreases in TH BMD of > 8%.

Lumbar spine BMD results were stratified by baseline T score (low baseline T score [≤ -1 and ≥ -2] versus normal baseline T score [> -1]), age (< 65 years vs. ≥ 65 years), and type of ADT (LHRH agonist alone vs. LHRH agonist with antiandrogen). Zoledronic acid-treated patients with low baseline T scores experienced greater increases in LS BMD compared with patients with normal baseline T scores (5.8% vs. 4.4%); the least squares mean differences between treatment groups were 8.7% (*P* = 0.0017) in patients with low BMD and 6.1% (*P* < 0.0001) in patients with normal BMD, suggesting that patients with low baseline BMD experienced greater benefit with zoledronic

Figure 2 N-Telopeptide and Bone-Specific Alkaline Phosphatase Levels Increased in the Placebo Group



Least squares mean (standard error of the mean) percentage change from baseline in NTX and BSAP levels in men with locally advanced prostate cancer receiving androgen deprivation therapy and zoledronic acid or placebo. P values correspond to the difference in the percentage change between groups (zoledronic acid vs. placebo) at each time point.

acid. No significant differences in LS BMD changes over time occurred with zoledronic acid when LS BMD results were stratified by age or type of ADT.

At baseline, 82 (77.4%) zoledronic acid–treated patients and 91 (83.5%) placebo-treated patients had LS T scores > -1. By week 52, T scores in 8% of placebo-treated patients with baseline T scores > -1 decreased to between ≤ -1 and ≥ -2, whereas no zoledronic acid–treated patients experienced similar T-score decreases. At baseline, 22 zoledronic acid–treated patients (20.8%) and 16 placebo-treated patients (14.7%) had T scores between ≤ -1 and ≥ -2. In the placebo group, the T scores in 4 patients (25%) progressed to < -2 at week 52; similar progression was not observed in zoledronic acid–treated patients. One patient, who received placebo, developed a T score of < -2.5 (meeting the World Health Organization definition of osteoporosis). Lumbar spine T scores improved to > -1 in significantly more patients with baseline T scores between ≤ -1 and ≥ -2 in the zoledronic acid group compared with the placebo group (36% vs. 13%; P = 0.04).

By the end of study, zoledronic acid–treated patients experienced a mean increase in LS and TH T scores of 0.5 and 0.1 from baseline, respectively; T scores in patients receiving placebo decreased (LS, -0.2; TH, -0.2).

Markers of Bone Turnover

At week 52, patients receiving zoledronic acid experienced least squares mean decreases of 20% (SE, 4.76) and 37% (SE, 2.98) in NTX and BSAP levels, respectively (P < 0.0001, for both). In the placebo group, NTX and BSAP levels increased by 42% (SE, 4.57) and 16% (SE, 2.89; P < 0.0001, for both; Figure 2). Significant differences between the zoledronic acid and placebo groups in least squares mean NTX and BSAP levels were observed at each visit, with the magnitude of difference increasing for NTX (-27% to -62%; P < 0.0001) and BSAP (-28% to -52%; P < 0.0001) levels throughout the study.

Zoledronic acid–treated patients with low baseline T scores (≤ -1 and ≥ -2) experienced greater suppression of NTX levels throughout the study, compared with patients with normal baseline T scores (> -1). The least squares mean differences between treatment groups at week 52 were -82.7% (P = 0.0006) in patients with low BMD and -58.4% (P < 0.0001) in patients with normal BMD, again suggesting that patients with low baseline BMD experienced greater benefit with zoledronic acid. The type of ADT did not significantly influence the magnitude of NTX level suppression. Interestingly, neither baseline T scores nor type of ADT influenced the magnitude of BSAP level suppression. Zoledronic acid–treated patients aged < 65

years experienced slightly greater suppression of NTX and BSAP levels compared with patients aged ≥ 65 years. The least squares mean differences in NTX levels between treatment groups at week 52 were -72.3% and -56.9% for patients aged < 65 years and aged ≥ 65 years, respectively; for BSAP levels, these differences were -55.4% and -51.1% . Bone turnover marker level decreases stabilized by week 36 for NTX levels and by week 24 for BSAP levels in patients aged < 65 years receiving zoledronic acid; patients aged > 65 years experienced a gradual suppression of NTX and BSAP levels throughout the study.

In the zoledronic acid group, significant negative correlations between percentage changes in LS BMD and NTX levels ($r = -0.25$; $P = 0.04$) and TH BMD and BSAP levels ($r = -0.28$; $P = 0.02$) were observed. Correlations between percentage changes in LS BMD and BSAP levels ($r = -0.20$; $P = 0.09$) and TH BMD and NTX levels ($r = -0.19$; $P = 0.11$) were not significant.

Safety

The incidence and types of AEs were similar between treatment groups. The most common AEs included flulike illness (15% vs. 3%), fatigue (10% vs. 6%), and pyrexia (10% vs. 0) for the zoledronic acid and placebo groups, respectively. Serious or significant AEs occurred in 24 patients (21%) receiving zoledronic acid and 22 patients (20%) receiving placebo. The most common grades 3/4 AEs were musculoskeletal and connective tissue disorders (4% vs. 3%), general or administration site disorders (4% vs. 1%), and nervous system disorders (1% vs. 4%) for the zoledronic acid and placebo groups, respectively. One patient in each group experienced acute renal failure; blinded investigators assessed these events as unrelated to the study drug in the zoledronic acid–treated patient and possibly related to the study drug in the placebo–treated patient. Two patients in each group experienced notable increases in S-Cr levels, but zoledronic acid–treated patients experienced smaller increases (0.5 mg/dL each) than did patients receiving placebo (0.6 mg/dL and 0.9 mg/dL). Osteonecrosis of the jaw was not reported in either group. Trauma-related fractures occurred in 2 patients (2%) receiving zoledronic acid and 3 patients (3%) receiving placebo; nontraumatic fractures were not observed in either treatment group. The incidence of AEs requiring therapy discontinuation was similar between the zoledronic acid and placebo groups (7% vs. 6%). Four percent of patients receiving zoledronic acid and 5% of patients receiving placebo discontinued therapy because of serious AEs; none of the serious AEs in the zoledronic acid group were attributed to the study drug. One death in the zoledronic acid group was assessed as unrelated to the study drug.

Discussion

Bone loss and related complications occur more frequently and rapidly in patients with prostate cancer receiving ADT compared with those not receiving ADT.^{10,14} Consequently, patients with nonmetastatic prostate cancer receiving ADT are 20%–35% more likely to experience traumatic and nontraumatic (ie, osteoporotic) fractures.^{8,15,16} Shahinian and colleagues performed a longitudinal study using patients with prostate

cancer included in the linked National Cancer Institute's Surveillance, Epidemiology, and End Results program and Medicare databases and reported a relative fracture risk of 1.37 (95% CI, 1.2–1.57) in patients with nonmetastatic disease who received ≥ 9 doses of ADT within the first 12 months of diagnosis compared with patients not receiving ADT.¹⁵ Patients with prostate cancer who experience nontraumatic fractures also have a lower quality of life and higher mortality rate than do patients who do not experience fractures. For example, patients with prostate cancer receiving ADT are more likely to require fracture-related hospitalization during ADT (4.9% vs. 2.2%; $P < 0.001$). Additionally, Oefelein and colleagues reported a negative correlation between skeletal fractures and survival time in patients with prostate cancer receiving ADT, suggesting that prevention of skeletal fractures might improve survival.⁵

The risk of bone loss in men with prostate cancer is highest during the first year of ADT, with 1-year bone loss rates of 2.2%–4.8% in the LS and 0.6%–3.7% in the TH.^{10,17} The presence of osteoporosis risk factors other than ADT, such as advanced age, low vitamin D levels, and low dietary calcium intake, is common in patients with prostate cancer.¹⁸ Approximately 75% of patients in our study had ≥ 3 baseline osteoporosis-related risk factors, including ADT, suggesting that these patients were at a higher risk for fracture than those with ≤ 1 risk factor other than ADT at baseline. Therefore, initiating bisphosphonate therapy concurrently with or during the first year of ADT to reduce the risk of bone loss and related complications was warranted.

Although the difference in fracture risk between treatment groups is the most clinically relevant endpoint in clinical trials evaluating bone-loss therapies, several studies have shown that BMD is a robust surrogate marker for fracture risk in men with prostate cancer.^{18–20} For example, Kanis and colleagues reported a 40%–50% increase in the 10-year probability of nontraumatic fractures for each SD decrease in T score for men aged 70 years.¹⁹ Nontraumatic fractures were not observed in our study, although the study was not powered or designed to detect differences in fracture incidence. Whereas zoledronic acid has been shown to delay and prevent skeletal complications in patients with prostate cancer with bone metastasis, whether the drug would provide patients with nonmetastatic prostate cancer receiving ADT with similar benefits remains unknown.^{21,22}

Smith and colleagues showed that zoledronic acid effectively prevents bone loss in patients with prostate cancer when ADT and zoledronic acid are initiated concurrently, reporting 5.6% and 1.1% increases in LS and TH BMD, respectively, in patients after 1 year of zoledronic acid therapy.¹¹ These investigators did not evaluate whether zoledronic acid initiated during the first year of ADT could reverse existing bone loss or prevent further ADT-related bone loss, the effect of zoledronic acid on bone turnover markers, or the benefit of zoledronic acid in patients with low versus normal baseline T scores.

After 1 year of zoledronic acid (4 mg I.V. every 3 months) therapy, we observed significant increases in LS (4.7%) and TH (1.6%) BMD in men with locally advanced prostate cancer who had received up to 12 months of ADT at the time zoledronic acid was initiated. In contrast, patients receiving placebo ex-

perienced significant decreases in LS (-2%) and TH (-2.1%) BMD. Although all patients receiving zoledronic acid therapy experienced increased BMD, patients with low baseline T scores (≤ -1 and ≥ -2) experienced a greater magnitude of increase in LS BMD compared with patients with normal baseline T scores (> -1 ; 5.8% vs. 4.4%). Collectively, these study results show that zoledronic acid attenuates, prevents, and/or reverses ADT-induced bone loss when initiated during the first 12 months of ADT, with patients who have low baseline BMD experiencing the greatest benefit.

The relatively rapid and sustained suppression of serum NTX and BSAP levels observed in zoledronic acid-treated patients compared with placebo-treated patients further supports and substantiates zoledronic acid's ability to abrogate bone loss in this patient population. Also, it is consistent with the pattern of bone marker changes observed in a placebo-controlled, dose-determining study in postmenopausal women with osteoporosis receiving zoledronic acid, in a study evaluating zoledronic acid for the prevention of aromatase inhibitor-induced bone loss in patients with breast cancer, and in studies evaluating oral bisphosphonates for the prevention and treatment of postmenopausal osteoporosis.²³⁻²⁶ Furthermore, the magnitude of NTX level suppression was greatest in patients with low baseline T scores, suggesting that patients with pre-existing bone loss are more likely to benefit from zoledronic acid. Significant yet weak negative correlations between changes in LS BMD and serum NTX levels ($r = -0.25$; $P = 0.04$) and TH BMD and BSAP levels ($r = 0.28$; $P = 0.02$) were also observed. Study results have indicated that short-term decreases in urinary NTX levels correlate with long-term increases in LS BMD ($r = -0.16$ to -0.53), suggesting that markers of bone turnover might be used as surrogate markers to monitor response to bisphosphonate therapy.^{24,27-29} Diurnal variations in serum NTX levels might have contributed to the weaker correlation observed in our study compared with other studies.³⁰

Zoledronic acid (4 mg I.V. every 3 months) was generally well tolerated. The rates of study discontinuation because of AEs were similar between the 2 groups; the rates of common AEs in the zoledronic acid group were consistent with rates previously reported for this drug.³¹ More patients receiving zoledronic acid than placebo withdrew consent; however, most of the consent withdrawals were not AE related.

Because patients with locally advanced prostate cancer receive several years of ADT, studies evaluating the safety and efficacy of zoledronic acid administration for > 12 months are needed. The Radiation Therapy Oncology Group is currently evaluating, in a large randomized, double-blind, placebo-controlled study, the safety and efficacy of zoledronic acid for the prevention of osteoporosis and associated fractures in patients receiving radiation therapy and long-term LHRH agonists for high-grade or locally advanced prostate cancer. This study will determine whether the benefit of zoledronic acid on BMD and fracture rate in this patient population is sustained over time. Furthermore, whether other zoledronic acid dosing schedules will produce similar results in this setting is unknown. Michaelson and colleagues recently reported the preliminary results of a small, randomized,

placebo-controlled trial evaluating the effects a single dose of zoledronic acid (4 mg I.V.) administered to patients with non-metastatic prostate cancer receiving ADT; the effects on BMD and NTX levels were similar to those observed in our study.³² At 12 months, LS (4% vs. -3.1%) and TH (0.7% vs. -1.9%) BMD increased in patients receiving a single dose of zoledronic acid and decreased in patients receiving placebo, respectively. N-telopeptide and BSAP levels also decreased (-17% and -13%) in patients receiving zoledronic acid and increased (10.8% and 15%) in patients receiving placebo (M.D. Michaelson, oral communication, July 2006). We observed a larger magnitude decrease in BSAP levels than that reported by Michaelson and colleagues (-37% vs. -13%) in patients receiving zoledronic acid; whether the different dosing schedules influenced these results is unknown. Larger studies confirming these results in men receiving annual zoledronic acid doses are warranted.

Conclusion

Zoledronic acid (4 mg I.V. every 3 months) was safe and effective in preventing bone loss and reducing bone turnover when initiated during the first year of ADT in patients with locally advanced prostate cancer. Based on the results of this study, initiation of zoledronic acid should be considered for all patients with prostate cancer during their first year of ADT, especially those with low baseline BMD.

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