Osteoporosis Management in Prostate Cancer Patients Treated with Androgen Deprivation Therapy

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BACKGROUND: The use of androgen deprivation therapy (ADT) for prostate cancer has increased substantially in recent years, exposing more men to potential treatment complications, including osteoporosis and fractures.

OBJECTIVE: To determine whether men treated with ADT for prostate cancer received osteoporosis screening, prevention, or treatment.

DESIGN: Cross-sectional observational study using a retrospective review of electronic medical records.

SUBJECTS: One hundred seventy-four patients with prostate cancer on ADT or status-post orchiectomy enrolled in primary care at the New Mexico Veterans Affairs Health Care System as of July 2005.

MEASUREMENTS: Patient demographics, tumor characteristics (Gleason score, stage, last PSA value, documented bone metastases), history of hip or vertebral fracture, osteoporosis risk factors (number of ADT shots, diabetes, smoking, heavy alcohol use or prescriptions for corticosteroids, thyroid hormone or dilantin). We defined recommended management as performing DXA scans or prescribing bisphosphonates, calcitonin, calcium or vitamin D.

RESULTS: Just 60 of 174 (34%) patients received recommended osteoporosis management based on DXA scans (13%) or treatment with oral or IV bisphosphonates (21%), calcitonin (1%), calcium (16%) or vitamin D (10%). On multivariate analysis, bone metastases, higher last PSA, and younger age at diagnosis were associated with recommended management, whereas Hispanic race/ethnicity was inversely associated.

CONCLUSIONS: Most men treated with ADT for prostate cancer did not receive osteoporosis screening, prevention or treatment. Evidence for advanced cancer though not risk factors for osteoporosis or fracture—was associated with receiving osteoporosis management. Further research is needed to identify optimal strategies for screening, prevention, and treatment in this population.

KEY WORDS: osteoporosis; prostate cancer; androgen deprivation therapy; screening; prevention; DXA scan.

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Prostate cancer is the most commonly diagnosed visceral malignancy and the second leading cause of cancer death in American men. In 2006, an estimated 234,460 new prostate cancer cases were diagnosed and 27,350 deaths were attributed to the disease.[1] Androgen deprivation therapy (ADT) is the mainstay of treatment for patients with locally advanced or metastatic prostate cancer.[2] However, the overall use of androgen deprivation has increased substantially because it is frequently being prescribed for men with early-stage disease.[3] Overall, more than 40% of newly diagnosed prostate cancer patients enrolled in the Cancer of the Prostate Strategic Urologic Research Endeavor received gonadotropin-releasing hormone (GNRH) agonists as an initial treatment.[4]

ADT raises the potential risk of adverse side effects from hypogonadism, including bone loss, osteoporosis, and increased fracture risk. In prospective clinical trials, bone loss rates in ADT-treated men with prostate cancer have been reported to range from 0.6% to 9% per year.[5–12] Retrospective studies in these men report fracture rates of 2.7% per year,[13] 20% at 10 years,[14] and 8 per 100 person-years at risk.[15,16] Prostate cancer patients who underwent bilateral orchiectomy had even higher fracture rates than age-matched controls during 15 years of follow-up: 40% vs 19% ($P<0.001$).[17]

Osteoporosis and related fractures in prostate cancer patients treated with ADT is particularly concerning because men have a higher risk than women for the adverse consequences of osteoporosis. Men have higher 1-year mortality rates after hip fracture than women[18] and they are at higher risk for undertreatment of hip fracture with antiresorptive agents after hospital discharge.[19] In addition, men with ADT-treated prostate cancer have worse survival after a skeletal fracture compared to those without a fracture.[20]

Expert guideline recommendations advocate evaluating men with ADT-treated prostate cancer for osteoporosis risk including family history of osteoporosis, low body weight, prior fractures, excessive alcohol use, smoking, glucocorticoid use, low vitamin D levels, and other medical comorbidities. In addition, the use of dual-energy x-ray absorptiometry (DXA) scan is recommended for patients beginning or receiving ADT, as is calcium and vitamin D supplementation.[21–24] Routine use of bisphosphonates is not recommended unless there is documented osteoporosis or fractures.[21,22]

Data on physician management of osteoporosis in ADT-treated prostate cancer patients are sparse, but suggest low rates of screening and treatment.[25] Osteoporosis intervention and treatment rates are similarly low in other high-risk male patient populations such as those with hip fracture,[19] steroid-treated rheumatoid arthritis,[26] and elderly men with fractures.[27,28] We evaluated a cohort of New Mexican veterans with ADT-treated prostate cancer to determine whether they received osteoporosis screening, prevention, or treatment.

METHODS

Study Cohort

The institutional Human Research and Review Committee approved the study protocol. We used an electronic clinical database to identify all New Mexico Veterans Affairs Health Care System patients diagnosed with prostate cancer as determined by ICD-9 diagnostic codes 185, 233.4, and 236.5, and who were currently enrolled in primary care as of July 2005 (n=1,667). Men who received chemical or surgical hormone deprivation were eligible for the study. We used an electronic pharmacy prescription database to identify the 171 men treated with ADT (leuprolide or goserelin). We also identified 6 men who underwent orchiectomy based on ICD-9 codes 62.3, 752.9 or CPT codes 54520, 54522, 54530, 54535, 54690, including 3 who were also treated with ADT. Overall, our cohort was comprised of 174 subjects.

Three reviewers abstracted electronic medical records with 1 reviewer (EY) supervising and checking records abstracted by the other 2 reviewers. Abstracted data included race/ethnicity, weight and height measured at the last clinic visit (body mass index [BMI] was calculated as kg/m^2), clinic site (Albuquerque hospital versus community-based outpatient clinic), date of prostate cancer diagnosis, and age at cancer diagnosis. Clinical prostate cancer data included the Gleason score, tumor stage (local, regional, distant, missing), last PSA value, and bone metastases confirmed by radiological imaging. We also abstracted data on history of a hip or vertebral fracture and osteoporosis risk factors, including number of ADT shots, prescriptions for medications predisposing to osteoporosis such as corticosteroids, thyroid hormone or phenytoin, diabetes, smoking, and heavy alcohol use (score of $\geq$4 on the Alcohol Use Disorder Identification Test-Consumption [AUDIT-C]).[29] Osteoporosis management was characterized based on performing DXA scans or prescribing oral or IV bisphosphonates, calcitonin, calcium or vitamin D. We recorded diagnoses of osteoporosis and osteopenia among patients who had these noted on x-ray, underwent DXA or had a fragility fracture.

Statistical Analysis

Statistical analyses were performed using SYSTAT (version 7.0). Descriptive statistics were reported as the means and standard deviations for normally distributed continuous variables and as frequencies for categorical values. We defined the dependent variable for our analyses as "recommended" osteoporosis management, based on the patient having undergone a DXA within 2 years before the last ADT shot or concurrently receiving prescriptions for a bisphosphonate, calcitonin, calcium or vitamin D during ADT treatment. Although guidelines suggest obtaining a baseline DXA,[21–24] we tailored our definition to reflect current management, a more clinically meaningful distinction given the duration of ADT treatment (mean 3.1±2.5 years). We also searched for any documentation in the medical record that the patient ever received pharmacological osteoporosis prevention or treatment or was evaluated with DXA (the health care system does not use ultrasound, CT or MRI to evaluate osteoporosis). We performed bivariate analyses to identify factors associated with recommended management. Continuous data were compared with T-tests and categorical data were compared with two-sample tests for binomial proportions or contingency table methods using chi-square tests. The Fisher's exact test was used when expected cell values were less than 5. P values $\leq$0.05 were considered statistically significant.

We performed a stepwise multivariate logistic regression analysis to identify factors associated with recommended management, including age at diagnosis, duration of cancer diagnosis, last PSA, race/ethnicity, BMI, number of ADT shots, bone metastases, history of hip or vertebral fractures, smoking, heavy alcohol use, diagnoses of diabetes, and prescriptions for corticosteroids, thyroid hormone, and phenytoin. We did not include tumor stage or Gleason score at diagnosis in the model because of the high proportions of missing data. Race was coded as non-Hispanic White, Hispanic, unknown or other (African American/Native American/Asian American were combined because of low sample sizes). We entered predictor variables using a forward and backward stepping procedure with an α<0.1 to enter and an α>0.1 to remove. All variables were retained in the final regression model if their improvement chi-square was <0.05.

RESULTS

Patient Characteristics

The study included 174 patients with a mean age at diagnosis of 70 years; 41% were non-Hispanic White (NHW), 36% Hispanic, 7% other, and 16% unknown. Among the subjects, 10% were diagnosed with osteoporosis, 15% were diagnosed with osteopenia, 11% had a hip or vertebral fracture, and 18% had bone metastases (Table 1). Overall, just 60 of 174 (34%) patients received recommended management based on recent DXA scans or concurrent pharmacologic treatment (Table 2). When we expanded our criteria for management to include ever receiving diagnostic testing or therapeutic interventions, still only 71 (41%) patients met this less stringent criteria for recommended management based on ever undergoing a DXA scan (16%) or ever being treated with oral or IV bisphosphonates (24%), calcitonin (1%), calcium (19%) or vitamin D (13%).

In patients with a DXA diagnosis of osteoporosis, 9 of 10 (90%) received pharmacologic management with bisphosphonates, calcitonin, calcium or vitamin D compared to 10 of 19 (53%) with a history of hip or vertebral fracture.

Significant univariate predictors of recommended management included younger age at diagnosis, higher last PSA value, greater number of ADT shots, being non-Hispanic White, corticosteroids prescription, and bone metastases (Table 3). On multivariate analysis, bone metastases, higher last PSA, and younger age at diagnosis were associated with recom-

Table 1. Patient Characteristics

Characteristics	*N*=174
Age at diagnosis (y)	70.2±8.4
Duration of cancer diagnosis (y)	6.3±4.0
Race	
Non-Hispanic White	72 (41%)
Hispanic	62 (36%)
Other*	13 (7%)
Unknown	27 (16%)
BMI	27.6±5.4
Concurrent medications	
Corticosteroids	29 (17%)
Thyroid hormone replacement	17 (10%)
Phenytoin	2 (1%)
History of orchiectomy	6 (3%)
History of hip/vertebral fracture	19 (11%)
Diabetes	38 (22%)
Cigarette smoking	28 (16%)
Alcohol	23 (13%)
Last serum PSA (ng/mL)	29.4±119.7
Number of ADT shots	8.5±6.8
Bone metastases	32 (18%)
Bone scan	121 (70%)
Characteristics	
Diagnosis of osteopenia	26 (15%)
Diagnosis of osteoporosis	17 (10%)
Clinic site	
Albuquerque	112 (64%)
CBOC	62 (36%)
Seen Heme Onc	69 (40%)

Values are mean (SD) unless otherwise noted.
*Other: African American, Native American, Asian American or Pacific Islander.

Table 3. Patient Characteristics Associated with Recommended Osteoporosis Management

Characteristics	Managed (*N*=60)	Not managed (*N*=114)	*P* value
Age at diagnosis (y)	68.4 (8.1)	71.2 (8.7)	0.04
Duration of cancer diagnosis (y)	7.5 (4.6)	6.6 (4.5)	0.24
Race			
Non-Hispanic White	36 (50.0%)	36 (50.0%)	0.0002
Hispanic	19 (30.6%)	43 (69.4%)	
Other*	4 (30.8%)	9 (69.2%)	
Unknown	1 (3.8%)	26 (96.2%)	
BMI	27.0±4.3	27.9±5.8	0.31
Gleason	7.0±1.3	6.8±1.2	0.63
Last PSA	74.6±194.8	5.4±18.2	0.0002
Number of ADT shots	10.1±7.1	7.6±6.5	0.02
Concurrent medications			
Corticosteroid	16 (55.2%)	13 (44.8%)	0.01
Thyroid hormone	6 (35.3%)	11 (64.7%)	0.94
Phenytoin	0 (0%)	2 (100%)	0.30
History of hip or vertebral fracture	9 (47.4%)	10 (52.6%)	0.21
Diabetes	13 (46.4%)	25 (53.6%)	0.97
Cigarette smoking	9 (47.4%)	19 (52.6%)	0.78
Alcohol	14 (93.3%)	1 (0.07%)	0.61
Bone metastases	23 (71.9%)	9 (28.1%)	<0.0001

Values are mean (SD) unless otherwise indicated.
*Other: African American, Native American, Asian American, or Pacific Islander

mended management. Being Hispanic was inversely associated with recommended management (Table 4). Significant factors associated with ever receiving osteoporosis management included presence of bone metastases, history of hip or vertebral fracture, younger age at diagnosis, lower BMI, and unknown ethnicity.

We also analyzed the data excluding all patients (n=32) with bone metastases as these men may be treated with bisphosphonates for reasons other than osteoporosis management. Only 26% of the 142 patients without metastases met the criteria for recommended osteoporosis management including 14% with a recent DXA scan and 12% who concurrently received oral or IV bisphosphonates. Overall, 34% met the less stringent criteria for ever receiving management. Younger age at diagnosis, higher last PSA value, greater number of ADT shots, and non-Hispanic White race remained significant univariate predictors of recommended management, whereas number of ADT shots and corticosteroids prescription did not. The only significant variable associated with recommended management in the multivariate analysis was a younger age at diagnosis.

DISCUSSION

In this study of 174 male veterans with ADT-treated prostate cancer, we found that only 34% had either a recent DXA or concurrent pharmacological interventions for osteoporosis prevention or treatment. Even with less stringent management criteria, only 41% of the patients ever received DXA testing or therapeutic interventions. After excluding subjects with metastases, only 26% of the cohort was currently being managed

Table 2. Evidence of Recommended Osteoporosis Management

Management	*N* (%) (*N*=174)
DXA scan	23 (13)
Oral or IV bisphosphonate	36 (21)
Calcitonin	2 (1)
Calcium	27 (16)
Vitamin D	17 (10)
Any of the above	60 (34)

Recommended: DXA within 2 years before the last ADT shot or concurrently receiving prescriptions for a bisphosphonate, calcitonin, calcium or vitamin D during ADT treatment.

Table 4. Variables Significantly Associated with Recommended Osteoporosis Management on Multivariate Analysis

Variables	Odds ratio (95%CI)	*P* value
Bone metastases	3.59 (1.22–10.50)	0.01
Last PSA	1.01 (1.00–1.03)	0.03
Age at diagnosis	0.95 (0.91–0.99)	0.02
Hispanic race	0.39 (0.18–0.86)	0.01

Other variables in the model included duration of cancer diagnosis, BMI, number of ADT shots, history of hip or vertebral fractures, smoking, heavy alcohol use, diagnoses of diabetes, and prescriptions for corticosteroids, thyroid hormone, and phenytoin.

Table 5. Bone Mineral Density Testing Recommendations for Men

Organization	Universal screening	Targeted screening —high risk	Risk factors
Osteoporosis Society of Canada[33]	No	Yes	Age over 65 Significant height loss Kyphosis Personal history of fragility fracture after age 40 Long-term use of glucocorticoids Clinical risk factors: hypogonadism, malabsorption, and primary hyperthyroidism
International Society for Clinical Densitometry[34]	No	Yes	Age 70 and older Fragility fracture Disease or condition associated with low bone mass or bone loss On medications associated with low bone mass or bone loss
Institute for Clinical Systems Improvement[35]	No	Yes	Fragility fracture Long-term glucocorticoid therapy Osteopenia Vertebral fracture Chronic disease/processes associated with bone loss (including pharmacotherapy with medications that cause hypogonadism) Prolonged hypogonadism Prolonged immobilization

for osteoporosis and 34% were ever managed. Whereas all subjects were at risk for osteoporosis because of their ADT treatment, a substantial proportion of even those with additional risk factors for osteoporosis or fracture, including diagnosis of diabetes, smoking, alcohol use or prescriptions for corticosteroids, phenytoin or thyroid hormone, were not evaluated or treated for osteoporosis.

Failing to appropriately address osteoporosis in men with ADT-treated prostate cancer is problematic because longer durations of treatment (1.9 years or more) are associated with increased risk for osteopenia, osteoporosis, and non-pathologic fractures.[30] The numbers needed to harm for a fracture occurrence 12 to 60 months after diagnosis of prostate cancer is estimated to be 28 for men treated with GNRH-agonist and 16 for orchiectomy.[31]

The reasons why prostate cancer patients on ADT are not evaluated for osteoporosis or provided pharmacological interventions are probably multifactorial. One potential problem is that bone mineral density testing guidelines for high-risk populations are not uniform.[32] Conflicting recommendations[33–35] (Table 5) may be confusing to providers and patients.[32] Although risk factor assessments can be used to identify patients for BMD testing, there is no consensus about the most important risk factors.[35] Primary care providers may be unaware that ADT-treated men with prostate cancer are at risk for osteoporosis. Furthermore, expert opinion guidelines for managing osteoporosis in these patients have been published only in cancer and urology journals.[21–24] Other barriers to osteoporosis screening include the paucity of clinical trial data assessing the efficacy of BMD testing for fracture prevention, the cost of testing, the limited availability of testing facilities, and the belief that results would not affect treatment decisions.[36,37]

Barriers to osteoporosis treatment include medication costs, potential adverse effects, and uncertainty about osteoporosis treatment efficacy in high-risk individuals.[38] Whereas there are effective treatments for male osteoporosis,[39,40] the Food and Drug Administration (FDA) has not specifically approved any agents for preventing or treating osteoporosis in men with ADT-treated prostate cancer. Zoledronate is FDA-approved for use in metastatic hormone-refractory prostate cancer because it decreased skeletal events (including pathologic fractures) in these patients.[41] In clinical trials with nonmetastatic prostate cancer patients on ADT, zoledronate increased mean bone mineral density,[11] IV pamidronate prevented bone loss,[12] and once-weekly oral alendronate prevented bone loss, substantially improved bone mass, and decreased bone turnover.[42]

Uncertainty about who is responsible for osteoporosis management in prostate cancer patients poses another problem. Prostate cancer care is often multidisciplinary and patients see primary care physicians, medical and radiation oncologists, and urologists. Calls have been made for primary care physicians and subspecialists to share responsibility for osteoporosis management in order not to miss screening, diagnostic, and treatment opportunities.[43] Whereas complicated cases of osteoporosis may benefit from specialist expertise,[44–46] a case can be made for primary care providers to take the lead in osteoporosis management because they are already providing other preventive services.[47] In addition, primary care providers will be managing newly recognized nonosteoporotic ADT complications, including diabetes and cardiovascular disease.[48]

The low rate of osteoporosis management we observed is consistent with 1 study we found addressing this issue. In Tanvetyanon's study,[25] which included men with bone metastases, only 14.7% of patients received at least 1 intervention for osteoporosis prevention or treatment, as defined by DXA scanning within the previous 3 years or bisphosphonates, vitamin D, calcium, calcitonin or estrogen within the past year. That population was drawn from a large, suburban hospital and was mostly non-Hispanic White (64%) or African American (23%), and the only predictor for receiving osteoporosis intervention was bone metastases. Our subjects differed substantially because we had a racially/ethnic diverse population (43% were Hispanic, Native American, African American or Asian American) and a large rural population (36%). Although both these studies involved veterans, limited management was consistently found across all races and ethnicities and for both urban and rural populations, suggesting that this is a wide spread issue in prostate cancer patients on ADT treatment.

There are several imitations of this study. As this was a retrospective chart review, accuracy of data was dependent on comprehensiveness of documentation and consistency of data abstraction. This study could not determine whether a provider's decision to order a DXA or prescribe medications such as calcium and vitamin D was influenced by the ADT treatment. Patients with bone metastases were more likely to receive IV bisphosphonates and see oncologists. Therefore, these treatments may have been for preventing pathologic fractures or treating hypercalcemia rather than for osteoporosis management. By including patients with bone metastases, we may have inflated the estimate of osteoporosis management related to ADT treatment. However, this allowed us to compare our results with the other study addressing this issue that we found in the literature.

We were also unable to ascertain why patients were not evaluated or treated for osteoporosis. Patient resistance has been documented even amongst groups that have sustained a low-impact fracture and are at high risk for future osteoporotic fractures.[49] Osteoporosis risk may be a low priority for patients within the context of their general health care.[50] We did not evaluate whether a limited life expectancy influenced clinical decisions regarding osteoporosis management. We examined charts from only one Veterans Administration system. Although this system included a main hospital and outlying community-based outpatient clinics (CBOCs), our results may not be generalizable to other sites. Although all study patients received ADT through the VA, many of the patients followed at the CBOCs have dual care. Based on chart reviews, we could not ascertain whether they received testing or medications from non-VA providers. The CBOCs do not have DXA scans at the facility, which could impact screening rates. Although Hispanic ethnicity significantly predicted receiving less appropriate management, we could not identify race or ethnicity for a substantial proportion of our subjects. Therefore, our findings regarding racial/ethnic disparities in osteoporosis management should be interpreted cautiously.

Our study demonstrated low rates of osteoporosis management for prostate cancer patients on ADT. These findings are concerning given the known increased risk for osteoporosis associated with ADT and the availability of effective treatments to prevent bone loss or increase bone mass in these patients. There are many potential barriers to osteoporosis management in this population. Further research is needed to determine optimal strategies for ensuring that men with ADT-treated prostate cancer receive appropriate screening, prevention, and treatment for osteoporosis.

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