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ORIGINAL RESEARCH

Utilization of bone densitometry for prediction and administration of bisphosphonates to prevent osteoporosis in patients with prostate cancer without bone metastases receiving antiandrogen therapy

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Abby Holt[1]
Muhammad A Khan[2]
Swetha Gujja[3]
Rangaswmy Govindarajan[3]

[1]Arkansas Department of Health, Little Rock, [2]White River Health System, Batesville, [3]Division of Hematology/Oncology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Background: Prostate cancer subjects with prostate-specific antigen (PSA) relapse who are treated with androgen deprivation therapy (ADT) are recommended to have baseline and serial bone densitometry and receive bisphosphonates. The purpose of this community population study was to assess the utilization of bone densitometry and bisphosphonate therapy in men receiving ADT for non-metastatic prostate cancer.

Methods: A cohort study of men aged 65 years or older with non-metastatic incident diagnoses of prostate cancer was obtained from the Surveillance Epidemiology End Results (SEER)-linked Medicare claims between 2004 and 2008. Claims were used to assess prescribed treatment of ADT, bone densitometry, and bisphosphonates.

Results: A total of 30,846 incident prostate cancer cases receiving ADT and aged 65 years or older had no bone metastases; 87.3% (n=26,935) on ADT did not receive either bone densitometry or bisphosphonate therapy. Three percent (n=931) of the cases on ADT received bisphosphonate therapy without ever receiving bone densitometry, 8.8% (n=2,702) of the cases on ADT received bone densitometry without receiving intravenous bisphosphonates, while nearly 1% (0.90%, n=278) of the cases on ADT received both bone densitometry and bisphosphonates. Analysis showed treatment differed by patient characteristics.

Conclusion: Contrary to the recommendations, bone densitometry and bisphosphonate therapy are underutilized in men receiving ADT for non-metastatic prostate cancer.

Keywords: prostatic neoplasms, androgen antagonists, bone densitometry, gonadotropin-releasing hormone, osteoporosis

Introduction

Prostate cancer is one of the most common malignancies diagnosed worldwide. Androgen deprivation therapy (ADT) by bilateral orchiectomy or gonadotropin-releasing hormone analogs, with or without antiandrogens, is indicated as front-line treatment in metastatic prostate cancer, as well as in the adjuvant setting following radical prostatectomy with nodal metastasis or radiation therapy, and occasionally in patients with localized disease.[1]

ADT has influence on many metabolic pathways but the most common side effect is reduction of bone density.[2–6] Prostate cancer usually spreads to the bone in metastatic disease, and treatment with intravenous bisphosphonates is commonly prescribed

Correspondence: Rangaswamy Govindarajan
Hematology/Oncology, CAVHS, Winthrop Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, 4301W Markham Slot 508, Little Rock, AR 72205, USA
Tel +1 501 686 8511
Fax +1 501 686 7474
Email govindarajanrang@uams.edu

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at this stage in order to reduce skeletal-related events.[7,8] Loss of BMD correlates with the duration of ADT but is more pronounced during the first year of therapy.[7–10] Men initiating ADT are recommended to have an assessment of risk factors for osteoporosis, calcium and vitamin D intake, lifestyle modifications, and baseline and serial BMD assessment while on ADT, along with bisphosphonate therapy.[1] There is evidence that loss of BMD is a strong predictor of fracture risk.[11] Treatment with bisphosphonates used to prevent osteoporotic fractures has been shown to increase bone mineral density (BMD).[12]

Although the National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines propose baseline BMD assessment and bisphosphonate therapy, there has been no systematic review of the utilization of these interventions by practicing physicians in the community. The current study evaluated bone densitometry (BD) and bisphosphonate therapy utilization patterns to prevent osteoporosis in this patient population.

Subjects and methods

A retrospective cohort study was conducted using a Surveillance Epidemiology End Results (SEER)-Medicare linked database of men aged 65 years and older with a diagnosis of non-bony metastatic prostate cancer between 2004 and 2007. Individuals with a diagnosis of non-metastatic prostate cancer were identified. Only those treated with ADT were included in the study.

Patient data were obtained from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF), and Medicare inpatient treatment claims were identified using National Claims History noninstitutional physician/supplier part B files (claims for preventive services and coverage for outpatient prescription services) and outpatient part B claims (outpatient services, prescriptions, and durable medical devices) from hospital facilities. SEER-linked patient data from the PEDSF file were unavailable for the year 2008 at the time of the study; so prostate cancer patient data were analyzed for 2004–2007 with linked Medicare treatment claims from 2004 to 2008. In order to limit our analysis to patients with no metastatic disease to bone, only prostate tumors coded as no metastasis and only localized tumors in the PEDSF file were included in the analysis. Medicare claims from the National Claims History physician and outpatient files were matched with PEDSF patient data by SEER case ID number to select prostate cancer cases that had ever received ADT as part of treatment. ADT was identified using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology Codes (CPT) in the Medicare physician and outpatient claims files. Coding used for orchiectomy included 54520, 54521, 54522, 54530 , and 54535 or ICD-9 code 624, and coding for goserelin, leuprolide, leuprolide implant, or triptorelin were identified as codes J1950, J9202, J9217, J9218, or J9219.[13] BMD assessment by dual-energy X-ray absorptiometry was identified using HCPCS or CPT codes 77080 or 77081.

Treatment with intravenous bisphosphonates such as pamidronate or zoledronic acid were identified using Medicare HCPCS codes J2430 and J3487 during the study period 2004–2008. Since the Medicare part D data for outpatient medications including oral bisphosphonates were only available from 2007 in the SEER Medicare files, they could not be utilized for the analysis. Oral bisphosphonates are generally poorly absorbed and have gastrointestinal side effects, leading to low patient adherence with these drugs.[14,15] Due to lack of adherence, intravenous bisphosphonates are preferred to oral bisphosphonates in this patient population. Oral bisphosphonate use was not captured because the Medicare database does not collect details of oral therapy.

The one-sided exact binomial test of proportion was used to determine if physician compliance with serial BMD assessment and bisphosphonate treatment in patients undergoing ADT is consistently ≥80%. A survey of practicing physicians with a response rate of 63% found that physician's self-reported adherence to the clinical guidelines was 77%.[16] Therefore, 80% adherence to the clinical guidelines was used in this study. Logistic regression analysis was used to determine treatment differences by patient characteristics such as age group, race, clinical stage, and SEER registry geographic region. SAS 9.3 (SAS Institute, Cary, NC, USA) was used to analyze differences in treatment practices. Further logistic regression analysis was also done to explore the relationship between history of bone fractures and bisphosphonate treatment, age, race, tumor stage at diagnosis, and duration of ADT. The study was approved by the institutional review board at the University of Arkansas for Medical Sciences.

Results

Among 157,974 newly diagnosed prostate cancer cases, 100,865 were aged 65 years and older and had no bone metastases from 2004 to 2007. Subjects who did not have ADT claims were excluded from the analysis. In total, 30,846 prostate cancer patients aged 65 years and older with no bone metastases receiving ADT were eligible for analysis (Table 1). Cases were analyzed by use of BD and parenteral bisphosphonate therapy. Neither BD nor parenteral

Table 1 Prostate cancer cohort on ADT receiving BD and intravenous BP treatment, 2004–2008

	All patients (n)	Received BD % (95% CI)	OR for BD (95% CI)	Received BP % (95% CI)	OR for BP (95% CI)	Received BD and BP % (95% CI)	OR for BD and BP (95% CI)
Total	30,846	2,980 (9.7) (9.33–9.99)		1,209 (3.9) (3.70–4.14)		278 (0.9) (0.08–1.01)	
Age at diagnosis, years							
65–69	7,091	8.1 (7.49–8.76)	1.0	3.6 (3.19–4.06)	1.0	0.9 (0.67–1.11)	1.0
70–74	8,365	9.9 (9.24–10.51)	1.2 (1.11–1.39)*	3.7 (3.29–4.10)	1.0 (0.86–1.21)	0.9 (0.74–1.15)	1.1 (0.76–1.48)
75–79	7,964	10.4 (9.69–11.03)	1.3 (1.17–1.46)*	3.9 (3.44–4.29)	1.1 (0.90–1.27)	0.8 (0.60–0.99)	0.9 (0.63–1.26)
80–84	4,967	10.9 (10.08–11.82)	1.4 (1.23–1.57)*	4.6 (4.06–5.19)	1.3 (1.07–1.54)*	1.1 (0.76–1.33)	1.1 (0.82–1.71)
85+	2,459	8.5 (7.40–9.60)	1.1 (0.89–1.24)	4.3 (3.51–5.11)	1.2 (0.95–1.51)	0.9 (0.49–1.22)	1.0 (0.59–1.58)
Race							
White	24,407	9.9 (9.50–10.24)	1.0	4.1 (3.81–4.31)	1.0	1.0 (0.83–1.08)	1.0
Black	3,415	6.4 (5.59–7.23)	0.6 (0.54–0.72)*	3.3 (2.76–3.97)	0.8 (0.68–1.00)	0.6 (0.31–0.81)	0.6 (0.36–0.93)*
Hispanic	924	8.9 (7.04–10.71)	0.9 (0.71–1.12)	3.3 (2.10–4.39)	0.8 (0.55–1.15)	1.4 (0.65–2.17)	1.5 (0.84–2.60)
Asian	1,229	14.9 (12.90–16.88)	1.6 (1.36–1.88)*	3.9 (2.82–4.99)	1.0 (0.72–1.29)	0.7 (0.26–1.21)	0.8 (0.39–1.49)
Other	842	10.1 (8.06–12.13)	1.0 (0.82–1.29)	3.0 (1.82–4.12)	0.7 (0.48–1.08)	0.5 (0.01–0.94)	0.5 (0.18–1.33)
Unknown	29	~	~	~	~	~	~
Stage							
T0–T1	13,704	9.0 (8.48 –9.43)	1.0	2.6 (2.41–2.95)	1.0	0.6 (0.48–0.74)	1.0
T2	14,295	9.6 (9.13–10.09)	1.1 (1.00–1.17)	4.2 (3.90–4.56)	1.6 (1.41–1.83)*	0.9 (0.76–1.07)	1.5 (1.14–1.97)*
T3	2,050	14.4 (12.90–15.98)	1.7 (1.49–1.96)*	7.4 (6.28–8.55)	2.9 (2.40–3.54)*	2.4 (1.73–3.05)	4.0 (2.78–5.66)*
T4	378	10.3 (7.25–13.38)	1.2 (0.84–1.64)	13.2 (9.81–16.64)	5.5 (4.04–7.59)*	~	~
Unknown	419	10.7 (7.78–13.70)	1.2 (0.89–1.68)	8.6 (5.91–11.28)	3.4 (2.39–4.88)*	~	~
SEER registries by US region							
West	13,394	11.4 (10.89–11.97)	1.0	4.6 (4.23–4.94)	1.0	1.2 (0.98–1.34)	1.0
Midwest	3,948	8.5 (7.62–9.35)	0.7 (0.64–0.81)*	4.5 (3.81–5.10)	1.0 (0.82–1.15)	1.5 (1.14–1.90)	1.3 (0.98–1.78)
Northeast	7,775	9.8 (9.09–10.41)	0.8 (0.76–0.92)*	3.3 (2.88–3.68)	0.7 (0.61–0.82)*	0.5 (0.36–0.67)	0.4 (0.31–0.63)*
South	5,729	6.2 (5.59–6.84)	0.5 (0.46–0.58)*	2.9 (2.43–3.29)	0.6 (0.52–0.73)*	0.4 (0.24–0.57)	0.3 (0.22–0.53)*

Notes: The table shows the percentage of prostate cancer patients aged 65 years and older who received ADT and the recommended osteoporotic preventive therapy, ie, BD and intravenous BP, by demographic and tumor stage characteristics (n=30,846). Overall, nearly 1% of the study subjects on ADT received the recommended BD and BP therapy. ~, cells with ≤11 are suppressed in adherence with SEER-Medicare data use agreement. *P-value <0.05.
Abbreviations: ADT, androgen deprivation therapy; BD, bone densitometry; BP, bisphosphonates; CI, confidence interval; OR, odds ratio; SEER, Surveillance Epidemiology End Results.

bisphosphonate therapy were utilized in 87.3% (n=26,935) of subjects on ADT (Table 2). The age group, race, T stage, and geographic distribution are shown in Table 1, and for every covariate (age, race, T stage, and geographic location), the percentage of BD utilization and parenteral bisphosphonate administration was markedly low.

Table 2 Utilization of BD and BP in nonmetastatic prostate cancer cases aged ≥65 years and receiving androgen deprivation therapy (ADT) in 2004–2008

	BP therapy	No BP therapy	Total
Received BD	n=278	n=2,702	n=2,980
	0.90%	8.76%	9.66%
No BD	n=931	n=26,935	n=27,659
	3.02%	87.32%	90.34%
Total	n=1,209	n=29,637	n=30,846
	3.92%	96.08%	100.00%

Notes: The study population comprised 30,846 subjects. Approximately 10% (9.66%, n=2,980) of the patients received BD measurements, while nearly 4% (3.92%, n=1,209) of the patients received BP therapy. Overall, neither BD nor BP therapy were utilized in nearly 88% (87.32%, n=26,774) of subjects on ADT.
Abbreviations: BD, bone densitometry; BP, bisphosphonates.

Utilization of BD and intravenous bisphosphonate therapy

In our study, 8.8% (n=2,707) of subjects on ADT received BD assessments without ever receiving intravenous bisphosphonates. Three percent (n=931) of the cases on ADT received bisphosphonate treatment without ever receiving a BD assessment. Only 0.9% (n=278) of the subjects on ADT received both BD and bisphosphonates. A compliance rate of nearly 1.0% (0.9%), those subjects receiving both BD to screen for bone loss and preventive bisphosphonate therapy, was well below the expected rate of 80% (Table 2). Figure 1 shows the trend of BD and intravenous bisphosphonate utilization during the study period (2004–2008). Bisphosphonates were prescribed more often from 2006 but utilization remained low at below 10% for all years studied.

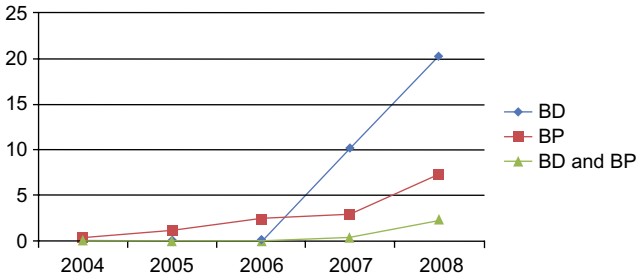

Figure 1 Trends in BD and intravenous BP utilization during the study period (2004–2008). BP was prescribed more often from year 2006, but utilization remained low at below 10% for the remaining years.
Abbreviations: BD, bone densitometry; BP, bisphosphonates.

Utilization of BD and intravenous bisphosphonates by patient characteristics

Odds ratios (ORs) show differences in preventive osteoporotic therapy by treatment category (Table 1). BD utilization increased with advancing age, except for those older than 85 years. BD utilization differed by race. Black men were less likely to receive BD than white men (OR 0.6; 95% confidence interval [CI] 0.54–0.72), and Asian men were more likely to have BD measurement performed than white men (OR 1.6; 95% CI 1.36–1.88). Patients diagnosed at later stages of disease (T3) received BD more often than men diagnosed with earlier stages of disease (T0–T1; OR 1.7; 95% CI 1.49–1.96). BD treatment differed by region. Men with prostate cancer living in the West region were more likely to receive BD than men living in any other region (Table 1). Patients in the Midwest, Northeast, and South regions were significantly less likely to receive BD than patients in the West, (OR 0.7; 95% CI 0.64-0.81, OR 0.8; 95% CI 0.76-0.92, and OR 0.5; 95% CI 0.46-0.58 respectively). Using the Midwest region as the reference group, patients in the West had 20% greater use of BD (OR 1.2; 95% CI 1.02–1.33).

Intravenous bisphosphonate therapy was prescribed more often to older men (80–84 years) than to younger men (aged 65–69 years; OR 1.3; 95% CI 1.07–1.54). Men diagnosed at later stages of disease (T2–T4) were more likely to receive bisphosphonate treatment than men diagnosed at earlier stages (T0–T1; Table 1). Men living in the Northeast and South regions were less likely to receive bisphosphonates than men living in the West region (Table 1).

Among men receiving the recommended treatment of BD and bisphosphonates, there were differences by race, tumor stage, and region. Black men were less likely to receive both BD and bisphosphonates compared with white men (OR 0.6; 95% CI 0.36–0.93). Advanced tumor stage was associated with treatment (Table 1). Men with prostate cancer in the Northwest and South regions were less likely to receive BD and bisphosphonates than men in the West region (Table 1).

Characteristics of study subjects with bone fractures

Only 25 of the 30,846 subjects in this study were identified to have a diagnosis of fracture based on ICD code in the SEER-Medicare database. Diagnosed bone fractures were identified using ICD-9 codes of 733.1 for osteoporotic fractures, and 808-809 for fractures to the spine or trunk. Logistic regression analysis was performed using bone fractures as the outcome variable. When controlling for age (a continuous variable), bisphosphonate treatment (a dichotomous variable), non-white race (a dichotomous variable with white race as the reference group), tumor stage (a dichotomous variable with T4 stage as the reference group), and duration of ADT (a continuous variable), an association between length of therapy and history of bone fractures was found. However, bone fracture was not associated with bisphosphonate therapy in this study population. In multiple studies, it has been demonstrated that ADT results in bone loss which could be a surrogate for increased skeletal-related events.[17–21] Although the duration of follow-up after diagnosis was short (≤5 years), continuous ADT increased the risk of bone fracture in this study cohort ($P \leq 0.05$). This population-level finding supports the clinical evidence of accelerated bone loss in patients receiving ADT.

Discussion

ADT has been shown to reduce disease progression and increase survival in subjects with prostate cancer.[22] BMD loss and osteoporosis is one of the main adverse effects of ADT in this population.[2–6,23] In this study, only a small proportion of prostate cancer patients on ADT were evaluated for bone loss, and an even smaller proportion ever received intravenous bisphosphonate therapy. Among the patient characteristics investigated, differences in age, race, tumor stage, and regional treatment were found.

Approximately 12% of men in the general population have osteoporosis.[24] Osteoporosis may be asymptomatic, but 20% of men on ADT have skeletal-related events such as fracture.[24] ADT has been associated with accelerated bone loss of up to 4.5% per year, and loss of BMD is considered a strong surrogate for increased risk of skeletal-related events.[2,4,5,19–22,25] The rate of bone loss is greatest in the first year of ADT, and osteoporosis is prevalent in nearly 50% patients on ADT by 4 years and 80% by 8 years.[8] Early BMD assessment and treatment may potentially prevent

fragility fractures, as recommended by national organizations such as the National Comprehensive Cancer Network and American Society of Clinical Oncology.[1,21,22,25] Prevention of bone loss, resulting in a reduction of skeletal-related events, may maintain good quality of life for patients with prostate cancer on ADT. Concurrent administration of a bisphosphonate or a selective estrogen receptor modulator has been shown to stabilize or increase BMD. In randomized studies, bisphosphonate therapy, including pamidronate, zoledronic acid, or alendronate, has been shown to improve BMD and decrease markers of bone metabolism in men on ADT.[4,5,7,20–29] This community-level study supports evidence that BD utilization and bisphosphonate therapy reduce fracture risk in men with prostate cancer receiving ADT. Intravenous bisphosphonate therapy, ie, zoledronic acid, has been evaluated in several studies, and was determined to be the best treatment to prevent bone loss in prostate cancer patients undergoing ADT.[30] Treatment with denosumab, which is currently recommended as an alternative to zoledronic acid for patients with nonmetastatic prostate cancer, was approved by the US Food and Drug Administration in 2011, and was not a treatment option during the study years examined.[31] Therefore, analysis of guideline compliance using intravenous bisphosphonates as a measure was appropriate for this study.

In addition, the cost of osteoporosis-related fractures among men in the USA is approximately $4.1 billion per year, and the effect on rising health care costs could potentially have an impact on the survival benefit of ADT in patients with metastatic prostate cancer. Subjects on ADT are recommended to be screened for fracture risk, with BMD testing at baseline, after 1 year of ADT, and then every 2 years or as clinically indicated.[32,33] In addition, counseling patients for fall risk and applying interventions to reduce falls may consequently reduce fracture risk in this population.

Most evidence supporting the use of bisphosphonates for prevention of ADT-related bone loss in men with prostate cancer is derived from studies evaluating intravenous bisphosphonates.[4,5,20,21] This is due to the lack of data available to analyze oral bisphosphonate use in large population studies. Greenspan et al recently demonstrated a significant increase in BMD in men with prostate cancer receiving ADT and once-weekly oral alendronate 70 mg.[22] Denosumab, another current treatment and unavailable during the study years examined, is recommended as an alternative to zoledronic acid for nonmetastatic prostate cancer patients.[31] The long-term use of oral bisphosphonate therapy could not be evaluated in this study because Medicare part D data are not available during the study period. However, due to lack of patient adherence, oral bisphosphonates have not been the preferred treatment over intravenous bisphosphonates in this patient population, so likely did not significantly affect the outcome.[14,15]

Our study re-emphasizes the importance of using BD measures to evaluate skeletal integrity and prevent osteoporosis with the utilization of bisphosphonates among patients who are on ADT. There seems to be a lack of understanding regarding the implications of ADT for prostate cancer.

Conclusion

Although the follow-up time was short, continuous ADT was associated with an increased risk of bone fracture, which supports previous clinical studies concerning accelerated bone loss in patients receiving ADT. In this community population study, we demonstrated that a very small proportion of patients underwent evaluation for bone loss and an even smaller proportion of patients received bisphosphonates. In addition, even when overall treatment utilization is low, black men were less likely to receive the recommended treatment of BD and bisphosphonates compared with white men. Further, utilization practices differed by region, with men residing in the West and Midwest regions receiving optimum treatment of BD and bisphosphonates when compared with men in the Northeast and South. Contrary to the recommendations, screening for bone loss and preventive treatment practices among this community population was markedly low for every age group, race, stage at diagnosis (T0–T4), and SEER registries by US geographic region.

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Disclosure

The authors report no conflicts of interest in this work.

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