The Risk of Fracture in Patients Undergoing Androgen Deprivation May Be Overstated: Analysis of an Unselected Cohort of Patients

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Objective: In this study we examined the prevalence of fracture among men undergoing ADT for prostate cancer to determine if the fracture risk was increased among this population.

Background: Androgen deprivation therapy (ADT) is a therapeutic approach for men with various prostate cancer disease states. Treatment-related side effects of ADT include rapid bone loss. Previous studies have found that the bone loss related to ADT leads to the development of fractures.

Methods: This is a retrospective cohort study of patients treated with ADT in a radiation oncology and medical oncology practice at an urban academic medical center from 2005 to 2010. Patients with evidence of bone metastases responsive to ADT were included. Those with androgen-independent prostate cancer were excluded.

Results: One hundred thirty patients met the inclusion criteria and among them only three fractures occurred during 373 person-years of follow-up. The fracture-free survival (FFS) rate at three years for all was 97.7%. Excluding fractures occurring within six months of ADT initiation, the FFS rate was 100% at three years. No significant difference was demonstrated in those screened with a pretreatment dual-emission X-ray absorptiometry (DEXA) scan; there was no relationship between the number of ADT cycles, recovery of testosterone to normal, or total time on ADT. Older patients, surprisingly, had a lower risk ($p = 0.054$). Patients with normal bone mineral density (BMD) had an FFS rate of 93.8% at three years, osteopenic patients had 94.7%, and patients with osteoporosis and hormone-responsive metastases had 100%.

Conclusion: The prevalence of fracture among this group is significantly less than what has previously been reported for men receiving ADT, potentially suggesting an overstatement of risk in the literature to date. Further prospective study with a larger sample size is needed.

INTRODUCTION

Prostate cancer is the most common newly diagnosed cancer in the United States. It represents 28% of the estimated 1.5 million cancers diagnosed in 2010 and is the cause of 11% of cancer-related deaths among men (Jemal, Siegel et al. 2010). Androgen deprivation therapy (ADT) is the main therapeutic approach for men with metastatic prostate cancer and it also plays a role in locally advanced disease in combination with radiotherapy to prevent recurrence (Bolla, Gonzalez et al. 1997). The use of ADT for localized prostate cancer has gained popularity, increasing from approximately 3.7% of all patients in 1991 to 30.9% in 1999 to nearly 50% in a 2002 cohort (Meng, Grossfeld et al. 2002; Shahinian, Kuo et al. 2005b). Treatment-related side effects can influence quality of life; they include weight gain, loss of lean muscle mass, impaired concentration, decreased libido, and hot flashes (Celestia 2004). Numerous studies have shown that patients treated with ADT experience rapid bone loss (Berruti, Dogliotti et al. 2002; Diamond, Higano et al. 2004; Smith, Lee et al. 2004). More recently, two studies reported that the bone loss related to ADT increases the risk of development of fractures (Shahinian, Kuo et al. 2005a; Smith, Peart et al. 2006). In this study we examined the prevalence of fracture among men undergoing ADT for prostate cancer to determine if the fracture risk was increased among this population.

METHODS

This is a retrospective cohort study of patients treated with ADT in a radiation oncology and medical oncology practice at an urban academic medical center from 2005 to 2010. The study included 130 men who received ADT as primary or adjunct therapy for prostate cancer. Patients with evidence of bone metastases responsive to ADT were included, while those with androgen-independent prostate cancer were excluded. Patients who were treated with ADT during the years of the study who had also been treated previously with ADT were included, and all their ADT treatment courses were analyzed. The primary study outcome was any clinical fracture with radiographic documentation at any time following the initiation of ADT. The study protocol was reviewed and approved by the St. Luke's–Roosevelt Hospital Center Institutional Review Board.

Statistical Analysis

Kaplan-Meier analysis was used to generate estimates of FFS rates. Differences between Kaplan-Meier estimates of two groups were compared using the log-rank statistic. Multivariate analyses were performed with the use of Cox proportional-hazards regression. Factors analyzed were: presence or absence of testosterone recovery after ADT discontinuation, age, presence of osteoporosis-related comorbidities (history of fracture as adult,

diabetes, smoking, heavy alcohol use, low body weight, renal disease), use of medication linked to osteoporosis (glucocorticoids, thyroid hormone, anticonvulsants, chronic heparin therapy, loop diuretics, methotrexate, proton-pump inhibitors, selective serotonin reuptake inhibitors), race, presence of metastases, number of follow-up visits, duration of follow-up, and duration of ADT. In addition, secondary analysis was performed looking at the impact of bone densitometry screening on the incidence of fracture. Analysis was performed using the SPSS Statistics program v. 14.0.

RESULTS

One hundred thirty patients met the criteria for inclusion in the study. Their characteristics are listed in Table 1.

The primary endpoint of fracture was experienced by 3 of the 130 patients. The details of these fractures are listed in Table 2. All of the fractures occurred soon after ADT initiation, with five months being the longest duration of treatment prior to fracture. Further, all fractures occurred following falls and none occurred in patients with metastatic disease.

The FFS rate for all patients at three years was 95.1%. If fractures that occurred within six months of ADT initiation, which were unlikely to be related to ADT, are excluded, the FFS rate was 100%. When the cohort was stratified based on bone mineral density (BMD) screening, two of the three fractures occurred among those monitored with DEXA scans. The difference in FFS between those screened with DEXA scans prior to ADT versus those not screened was not significant. Surprisingly, the fractures did not correlate with worse BMD measurements, as might be expected. At three years, patients with normal BMD had an FFS rate of 93.8%, osteopenic patients had an FFS of 94.7%, and patients with osteoporosis and hormone-responsive metastases had an FFS of 100%. These differences were not statistically significant.

One hundred ten patients underwent a single course of ADT. Among those, the median duration of therapy was nine months. Two fractures occurred within the group undergoing only one course of treatment (9 months and 31 months of ADT, respectively). However, the expected dose-response relationship that has been previously demonstrated did not manifest in our cohort, as both fractures occurred within the first five months of ADT initiation. Furthermore, among the 20 patients who received more than one course of treatment (median 36 months), only one fracture occurred. This fracture was traumatic and occurred three months after ADT initiation.

Bone densitometry was performed on 41 patients; it identified 6 patients as osteoporotic, 19 as osteopenic, and 16 with normal BMD. Among the monitored

TABLE 1. CHARACTERISTICS OF THE PATIENTS

Age at Diagnosis (y)	67.7 ± 1.3
Race	
Black	27.7%
Hispanic	26.1%
White	35.4%
Other	10.8%
Median Follow-up Visits (n)	15
Median Follow-up (m)	26
Total Follow-up (person-months)	4474
AJCC Stage (n)	
I	16
II	84
III	22
IV	8
Gleason Score (n)	
5–6	32
7–8	79
9–10	18
Unknown	1
Total ADT Duration (m)	
<6	13
6–8	39
9–12	49
>12	29
Courses of ADT (n)	
1	110
2	4
3	11
>3	5
Presence of Osteoporosis Risk Factors	
Lifestyle/medical	53.85%
Medication	20.77%
Other Treatments (n)	
IMRT	107
Brachytherapy	15
Both	4
Testosterone Recovery to Normal	62.8%
Pretreatment DEXA Scan	31.5%

n = number, y = years, m = months

TABLE 2. FRACTURE CHARACTERISTICS			
	Fracture 1	Fracture 2	Fracture 3
Types of Fracture	Fracture of ankle s/p fall	Fracture of R 8th & 9th rib and R inferior orbit s/p fall	Fracture of ankle s/p fall
Length of Time from ADT Initiation to Fracture (m)	3	3	5
Comorbidities	None	None	SSRI use
Demographic	50 y/o Caucasian	61 y/o AA	64 y/o Caucasian
Metastatic Disease	No	No	No

TABLE 3. ACTUAL VS. EXPECTED FRACTURES	
	Fractures
Observed	3
Expected (Shahinian et al.)	25.22
Expected (Smith et al.)	29.49

patients, five of the six osteoporotic patients (one declined), three of the osteopenic patients, and one with normal BMD (whose use predated ADT initiation) received treatment with a bisphosphonate. None of the nine in the bisphosphonate treatment group experienced a fracture during follow-up.

Secondary analyses were also performed, specifically looking at testosterone recovery, age, presence of osteoporosis risk factors (lifestyle, medical, or medication), race, presence of metastases, number of follow-up visits, duration of follow-up, or duration of ADT, and the relation of these factors to fracture. None of the analyses demonstrated a statistically significant difference between the two groups, although older patients, surprisingly, demonstrated a strong trend toward lower fracture risk ($p = 0.054$).

DISCUSSION

In our cohort of patients, the fracture prevalence of men receiving ADT was significantly less than previously reported in large population-based studies. Shahinian and colleagues found fracture prevalence to be nearly 20% , while Smith and colleagues reported that the rate of any fracture was 7.91/100 person-years at risk for men receiving ADT. Our study had a fracture prevalence of 2.3% and a rate of 0.8/100 person-years. Based on the reported rate of fracture from those two previous studies, our group had markedly fewer than was anticipated (Table 3). Further, all of our fractures, which occurred within five months of initiation of treatment, would not have been included in the Shahinian et al. (2005a) study. We included the fractures in the first year, as the data show that the most accelerated bone loss occurs in the first six months following the initiation of ADT (Greenspan, Coates et al. 2005).

In addition to analyzing fracture incidence in terms of person-years, we looked at fractures using Kaplan-Meier estimates. Shahinian et al. (2005a) had a three-year FFS rate of approximately 90% within their group that received one to four doses of ADT, while the group that received greater than nine doses had an FFS rate of about 85%. This is in stark contrast to our results, which demonstrated an overall three-year FFS rate of 95.1%, with 90% of our cohort receiving at least six months of ADT. Furthermore, the FFS rate increased to 100% if we eliminated fractures occurring within the first 12 months as in the Shahinian study.

There are a number of potential explanations for the marked difference demonstrated in our cohort versus the previous studies. One possibility is that the patients in this study were on average younger than those in the other studies, and age has previously been reported as a risk factor for increased fracture risk, despite the opposite finding in our cohort (Kanis 2002). Our study had a more racially diverse population when compared with the predominantly Caucasian groups seen in the previous studies, and Caucasian race has also been shown to increase fracture risk (Baron, Barrett et al. 1994). Lastly, physician discretion has the potential to affect results. Compared with the large population-based studies that included patients from 1992 to 1997 (Shahinian, Kuo et al. 2005a) and 1998 to 2003 (Smith, Peart et al. 2006), this study included patients of only two physicians from 2005 to 2010. These physicians perhaps had greater discretion in prescribing ADT to their patients, based on comorbidities and the literature suggesting a correlation between ADT and bone health as early as 1995 (Eriksson, Eriksson et al. 1995).

This study also failed to demonstrate a benefit from screening patients with DEXA scans prior to ADT. Undoubtedly, preventing fractures in men undergoing ADT is necessary, as fractures have been shown to increase cost of care (Krupski, Foley et al. 2007) and decrease length of survival (Oefelein, Ricchiuti et al. 2002). A 2010 study using a Markov state-transition model even suggested that the use of DEXA screening is cost effective in preventing fractures (Ito, Elkin et al. 2010), but the data from this study call that into question.

The retrospective design of this study is a limitation. Also, the cohort of patients was limited in number and geographically confined to one hospital. Duration of patient follow-up, while the same as in the Smith study, was a limiting factor. Lastly, the number of fractures in the study cohort limits the analysis and conclusions regarding DEXA screening.

In conclusion, the prevalence of fracture in the study group is significantly less than what has previously been reported for patients receiving ADT, potentially suggesting an overstatement of risk. Further prospective study with a larger sample size is needed.

REFERENCES

Baron, J.A., Barrett, J., Malenka, D., Fisher, E., Kniffin, W., Bubolz, T., and Tosteson, T. (1994). Racial differences in fracture risk. *Epidemiology* **5**(1):42–47.

Berruti, A., Dogliotti, L., Terrone, C., Cerutti, S., Isaia, G., Tarabuzzi, R., Reimondo, G., Mari, M., Ardissone, P., De Luca, S., Fasolis, G., Fontana, D., Rossetti, S.R., and Angeli, A. (2002). Changes in bone mineral density, lean body mass and fat content as measured by dual energy X-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* **167**(6):2361–2367.

Bolla, M., Gonzalez, D., Warde, P., Dubois, J.B., Mirimanoff, R.O., Storme, G., Bernier, J., Kuten, A., Sternberg, C., Gil, T., Collette, L., and Pierart, M. (1997). Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* **337**(5):295–300.

Celestia, S. H. (2004). "Understanding treatments for bone loss and bone metastases in patients with prostate cancer: a practical review and guide for the clinician." *The Urologic clinics of North America* **31**(2): 331-352.

Diamond, T.H.,, C.S., Smith, M.R., Guise, T.A., and Singer, F.R. (2004). Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: Recommendations for diagnosis and therapies. *Cancer* **100**(5):892–899.

Eriksson, S., Eriksson, A., Stege, R., and Carlström, K. (1995). Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. *Calcif Tissue Int* **57**(2):97–99.

Greenspan, S.L., Coates, P., Sereika, S.M., Nelson, J.B., Trump, D.L., and Resnick, N.M. (2005). Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* **90**(12):6410–6417.

Higano, C.S. (2004). Understanding treatments for bone loss and bone metastases in patients with prostate cancer: A practical review and guide for the clinician. *Urol Clin North Amer* **31**(2):331–352.

Ito, K., Elkin, E.B., Girotra, M., and Morris, M.J. (2010). Cost-effectiveness of fracture prevention in men who receive androgen deprivation therapy for localized prostate cancer. *Ann Intern Med* **152**(10):621–629.

Jemal, A., Siegel, R., Xu, J., and Ward, E. (2010). Cancer statistics, 2010. *CA Cancer J Clin* **60**(5):277–300.

Kanis, J.A. (2002). Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* **359**(9321):1929–1936.

Krupski, T.L., Foley, K.A., Baser, O., Long, S., Macarios, D., and Litwin, M.S. (2007). Health care cost associated with prostate cancer, androgen deprivation therapy and bone complications. *J Urol* **178**(4 pt. 1):1423–1428.

Meng, M.V., Grossfeld, G.D., Sadetsky, N., Mehta, S.S., Lubeck, D.P., and Carroll, P.R. (2002). Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. *Urology* **60**(3 suppl.1):7–11.

Oefelein, M.G., Ricchiuti, V., Conrad, W., and Resnick, M.I. (2002). Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol* **168**(3):1005–1007.

Shahinian, V.B., Kuo, Y.F., Freeman, J.L., and Goodwin, J.S. (2005a). Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* **352**(2):154–164.

Shahinian, V.B., Kuo, Y.F., Freeman, J.L., Orihuela, E., and Goodwin, J.S. (2005b). Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer* **103**(8):1615–1624.

Smith, M.R., Lee, W.C., Krupsi, T., Brandman, J., Wang, Q., Botteman, M., Pashos, C., and Litwin, M. (2004). Association between androgen deprivation therapy and fracture risk: A population-based cohort study in men with non-metastatic prostate cancer. *J Clin Oncol (Meeting Abstracts)* **22**(14 suppl.):4507.

Smith, M.R., Boyce, S.P., Moyneur, E., Duh, M.S., Raut, M.K., and Brandman, J. (2006). Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol* **175**(1):136–139.

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