Fractures in Jamaican Males with Prostate Cancer: A Retrospective Case Series

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ABSTRACT

Objective: Androgen deprivation therapy (ADT) reduces bone mineral density in men treated for prostate cancer. We sought to determine if there was an ethnic difference in fractures induced by ADT in Jamaican men.

Methods: A retrospective analysis of orthopedic admissions to the University Hospital of the West Indies from 2000- 2009 was done. Eligible patients had a history of prostate cancer and ADT. Etiology of fractures was determined. Methods of treatment of prostate cancer and clinico-pathological data were extracted from medical records.

Results: There were 13 admissions for fractures during the period and all were due to metastases. The mean duration of ADT use was 16.4 ± 19.0 (Range: 1-72) months. Conjugated estrogens were the most frequently used method of ADT however 55% of patients were exposed to multiple types of ADT.

Conclusion: Fractures in Jamaican men with prostate cancer are rare and associated with metastatic disease.

Keywords: Androgen deprivation therapy, bone mineral density, fractures, prostate cancer

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INTRODUCTION

A total number of 1042 new cases of prostate cancer were recorded in the Kingston and St. Andrew region of Jamaica between 2003 and 2007 (1). This accounted for approximately 41% of all new cancers diagnosed in males in urban Jamaica. The burden of prostate cancer in Jamaica is great with a reported incidence rate of 78.1 per 100,000 men and mortality rate of 53.9 per 100,000 men (1, 2). Prostate cancer has been ranked as the leading cause of cancer in Jamaica over the past 3 decades (3).

Bone disease is common in men with prostate cancer (4). This may be due to osteoporosis secondary to androgen deprivation therapy (ADT) or metastatic disease that is still seen commonly in Jamaica. ADT is used widely in the treatment of locally advanced or metastatic prostate cancer as well as an adjuvant to external beam radiation therapy (5-7). It has also been found to be beneficial in men with nodal metastases after radical prostatectomy (8). Its use has also widened in elderly men with localized prostate cancer or in cases of biochemical recurrence post-curative treatment of localized prostate cancer (9). From 2000- 2007, 458 patients, representing approximately 67% of cases of prostate cancer were treated with ADT at the University Hospital of the West Indies, Kingston, Jamaica (10).

Traditional methods of delivery of ADT are via surgical castration (bilateral orchiectomy) or medical castration (gonadotropin releasing hormone-GnRH agonists, GnRH antagonists and steroidal or non-steroidal anti-androgens). Conjugated estrogens, though not widely used due to possible cardiovascular toxicity may be administered parenterally as a form of ADT. Chronic treatment with all forms of ADT, except estrogens results in reduction of bone mineral density within 6 months of treatment (11). This increases rates of skeletal fractures and increases mortality (12).

Though there are demonstrable ethnic differences in bone mineral density, with persons of African descent having higher bone mass, this factor does not appear to be protective in African descent males on ADT for prostate cancer. We recently reported on decline in bone mineral density in Jamaican males with prostate cancer, treated with ADT (13). Although the association between ADT and osteoporosis has been established, we were still not aware of the burden of fractures in African-descent men on ADT for prostate cancer. Our aim was therefore to determine the burden and etiology of fractures in men treated with ADT for prostate cancer in Jamaica.

METHODS

Participants

This retrospective hospital-based case series included men with a histological diagnosis of adenocarcinoma of the prostate who were admitted to the Orthopedic Ward at the University Hospital of the West Indies, Kingston, Jamaica between January 1, 2000 and December 31, 2009. All patients were exposed to ADT.

Data collection

We reviewed data from patients' medical records as well as radiology films and reports. A Key exposure variable was the use of any form of ADT for prostate cancer. ADT was defined as exposure to surgical castration (bilateral orchiectomy) or medical castration (gonadotropin releasing hormone-GnRH agonists, GnRH antagonists, steroidal or non-steroidal anti-androgens and oral estrogens). Duration of ADT use was documented. Clinico-pathological data on prostate

cancer including age at diagnosis, initial prostate specific antigen (PSA) level and Gleason score were recorded. Gleason score 2– 4, 5–7 and 8–10 corresponded to well differentiated, moderately differentiated and poorly differentiated cancers, respectively. Key outcome variables were radiological diagnosis of fractures and prostate cancer-specific death.

Measures

Plain radiographs of all study patients were reviewed to determine the etiology and location of fractures. Fractures were classified as either due to metastases or osteoporosis. Sites of all metastatic deposits were recorded. Treatment of all orthopedic complications were recorded: radiation, surgery or conservative.

Analysis

Summary values are expressed as means with standard deviation or frequencies where appropriate. For categorical variables, we used Pearson's Chi squared statistics to assess association between exposure and outcome variables. We used multivariable logistic regression models to evaluate the association between exposure variables and the outcomes. Data were analyzed using Stata 12 for Windows (College Station, USA). The study was approved by the Ethics Committee, Faculty of Medical Sciences, University of the West Indies, Mona.

RESULTS

A total of 40 males with adenocarcinoma of the prostate were admitted to the Orthopedic Ward at the University Hospital of the West Indies, Kingston Jamaica during the study period. Table 1 summarizes the baseline characteristics of the patients.

Table 1: Baseline Characteristics of prostate cancer admissions to Orthopaedic Ward- University Hospital of the West Indies (2000–2009)

Variables	Mean ± (s.d.), median (IQR) or frequencies
Age	78.0 ± 10.1 years
PSA	201.0 ng/ml (IQR-510) (range: 2.8-14,260)
Gleason Score	7.9 ± 1.0
Well-differentiated (2-4)	0
Moderately differentiated (5-7)	34.6%
Poorly differentiated (8-10)	65.4%

Primary prostate cancer treatment

Only 2 patients had radical retropubic prostatectomy for treatment of initial localized prostate cancer.

Data on ADT use was available in 36 patients and all were exposed. Table 2 summarizes the frequencies and types of ADT used. Sixteen patients (44%) were exposed to a single type of ADT during the study period. However, 12 (33%) and 8 (22%) were exposed to 2 and 3 types of ADT, respectively. The mean duration of ADT use was 16.4 ± 19.0 (Range: 1-72) months.

Table 2: Androgen Deprivation Therapy (ADT) in Orthopaedic Admissions to the University Hospital of the West Indies (2000-2009)

Types of ADT	%
Surgical Castration	14 (38.9)
Anti-androgens	17 (47.2)
Luteinizing hormone releasing hormone (LHRH) analogue	9 (25.0)
Oestrogens	24 (66.7)

Fractures

There were 13 patients (32.5%) who were noted to have fractures. Radiological assessment revealed that all fractures were pathological and associated with bony metastases. The femur was the most common fracture site. No fracture was observed in the absence of metastatic deposits. Radiological evidence of metastases were evident in 33 patients. Fractures were treated with dynamic hip screws in 2 patients, an intramedullary nail in 1 patient and conservatively in the remaining patients. The remaining 27 patients who were not diagnosed with fractures were admitted for evidence of spinal cord compression or severe pain in association with metastatic disease. Eleven (11) patients received external beam radiation either for fractures or bony metastases.

There was no association between oestrogen use and the outcome of fractures. There was a trend towards association of LHRH use and fracture ($p=0.07$). Fourteen (14) had prostate cancer-specific deaths during the study period. There was no association between death and fractures.

DISCUSSION

The present study revealed a low fracture rate in Jamaican men with prostate cancer who were treated with ADT. In addition, there were no cases of osteoporotic fractures noted in these men. The results are in contradiction with large cohort and case control studies in other centers. In a large retrospective cohort study including 50, 613 men with prostate cancer listed in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare, of men surviving beyond 5 years of diagnosis there was a significantly increased risk of fractures in men exposed to ADT (19.4% versus 12.6%) (12). Similarly in a systematic review of skeletal adverse effects of ADT, the findings revealed that men on ADT for prostate cancer had an increased risk of overall fractures of 23% (RR- 1.23; [95% CI], 1.10-1.38) (14).

Prostate cancer is commonly seen in middle-aged and elderly males and these men are vulnerable to fragility fractures which increase with advancing age (15). There are genetic differences in osteoporosis with African ethnicity being protective (16). The Tobago Bone Health Study reported that bone mineral density was 10-20% higher in African Caribbean males compared to U.S. non-Hispanic black and white males, respectively (16). Nam et al demonstrated that these ethic differences were even greater when comparing Afro-Caribbean males to Asian males (17). Despite the advantage of a higher baseline bone mineral density in Afro-Caribbean men, the rate of decline with advancing age appears to be comparable between African-Caribbean and Caucasian males (18).

GnRH agonists which are the most commonly prescribed form of ADT in Jamaica and internationally, increase bone turnover by increasing parathyroid hormone-mediated osteoclast activation (10, 19, 20). Bilateral orchiectomy causes a similar accelerated bone turnover (21). Bone mineral density at the hip and spine reduces steadily at a rate of 2-3% annually in men

treated with ADT (22). There appears to be a similar decline in largely Afro-Caribbean populations. The Tobago Bone Health study reported a significant decline in bone mineral density in men with prostate cancer treated with ADT compared with their counterparts (18). We previously reported reduced bone mineral density in Jamaican men on ADT for prostate cancer compared to controls (13).

In spite of the osteoporosis that is induced by the hypogonadal state in these men, there is very little data on increased fracture risk in men of African ethnicity treated with ADT. Many of the reported large retrospective cohort studies evaluating fracture risk in men on ADT have men of African ethnicity underrepresented or perform no adjustment for the confounder of race in their analysis. Baseline data on the distribution of osteoporotic fractures in Jamaica show a preponderance of female patients with few fractures being due to the osteoporotic effect of ADT in prostate cancer patients (23, 24). We hypothesize that fractures due to ADT use in men of African ethnicity may be less common due to the protective effect of a higher initial bone mineral density.

Our results reveal that over 60% of patients were treated with the conjugated estrogen, Premarin® for prostate cancer. Oral estrogens found widespread use in the form of diethylstilbestrol many years ago in the management of patients with metastatic prostate cancer (25). The primary mechanism of action of estrogens was suppression of the hypothalamo-pituitary gonadal axis. Unfortunately, early studies with diethylstilbestrol utilized a high dose of 5 mg and this induced hepatic pro-coagulant proteins which increased thrombosis and cardiovascular events (26). These agents therefore have largely been replaced by GnRH analogues. However, their use is continued in Jamaica as the agents are cheap, appear to have minimal cardiovascular adverse effects and have been useful for second-line hormonal

manipulation. Estrogens are also directly cytotoxic to prostate cancer cells (27). Recent evidence suggests that parenteral estrogen administration maintains efficacy while avoiding cardiovascular toxicity (28, 29). Even more beneficial is the osteoporotic-sparing effect of estrogens (21). Estrogens maintain normal bone metabolism and since both osteoblasts and osteoclasts have estrogens receptors, their function is modulated by them (30, 31). The effect of estrogens on fracture risk is still unknown. There was no associated protective effect of estrogen use on fracture outcome in our study. This null effect could possibly be due to a small sample size. We suggest that the continued widespread use of oral conjugated estrogens in Jamaica for prostate cancer may offer protection from fractures in these men.

Our study had several limitations. Its retrospective nature precluded any assessment of fracture risk. This would have ideally been possible with a cohort or case-control study design. We are aware that our sample size of 40 men was small but it reflects the rarity of the condition in a setting where prostate cancer and ADT use is highly prevalent. Our study was a hospital-based and we are aware that this could provide a selection bias where asymptomatic fractures could be missed in patients not presenting to hospital, which is particularly likely in osteoporotic spinal fractures. Measurement bias could have occurred with the assessment of osteoporosis being made through radiographs and not DEXA at multiple sites. Misclassification could occur as the metastatic deposits could have developed after the osteoporotic fracture has occurred especially in the region of the spine where both pathologies are common. Due to the retrospective nature of the study, we were unable to assess for confounders such as glucocorticoid or alcohol use, other malignancies, endocrine disorders, activity level, smoking history or chemotherapy.

CONCLUSION

Osteoporotic fractures are uncommon in Jamaican males treated with ADT for prostate cancer. Additional cohort studies are needed to evaluate the effects of ADT in men of African-ethnicity.

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