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Atypical femur fractures among breast cancer and multiple myeloma patients receiving intravenous bisphosphonate therapy

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ABSTRACT

Purpose: Atypical femur fractures represent a potential complication of chronic oral bisphosphonate therapy in women with osteoporosis, but the risk of atypical femur fractures among cancer patients receiving intravenous bisphosphonates at higher cumulative doses remains unclear. We examined femur fractures occurring in cancer patients treated with intravenous bisphosphonates (IVBP) to determine whether a subset may be atypical fractures.

Methods: Between 2005 and 2010, we identified patients with known IVBP therapy for multiple myeloma or metastatic breast cancer, who subsequently sustained a femur fracture based on hospitalization, oncology, pharmacy and chemotherapy visit records. Radiographs were examined by an orthopedic surgeon to determine anatomic fracture site and pattern. An atypical fracture was defined as a transverse or short oblique fracture occurring below the lesser trochanter with evidence of focal hypertrophy of the lateral cortex and absence of biopsy-proven malignancy or radiation therapy at the fracture site.

Results: A total of 62 patients with breast cancer (N = 39) or multiple myeloma (N = 23) with femur fracture and prior IVBP treatment for bone malignancy were identified. There were 30 proximal hip, 18 subtrochanteric and 14 femoral shaft fractures. Intraoperative bone samples were sent in 29 of 58 fracture cases undergoing operative repair, with 76% positive for malignancy. Six cases (4 breast cancer, 2 multiple myeloma) of atypical femur fracture were identified, two with negative intraoperative pathology and four with no bone biopsy samples sent. Five of the six patients with atypical fracture had bilateral femur findings, including two with transverse fracture in the contralateral femur and three with focal hypertrophy of the contralateral cortex. Two atypical fracture cases also experienced osteonecrosis of the jaw compared to 3 in the remaining cohort (33% vs. 5%, $p = 0.07$). Patients with atypical fracture received more IVBP (median 55 vs. 15 doses) and zoledronic acid (32 vs. 12 doses) and had longer treatment duration (median 5.9 vs. 1.6 years) compared to patients without atypical fracture (all $p \leq 0.01$).

Conclusions: Among 62 patients who received IVBP for skeletal malignancy and experienced a femur fracture, we identified six cases of atypical fracture. While fractures in this population are often assumed to be pathologic, prospective studies investigating fracture pattern, microscopic bone pathology and pharmacologic exposures should be conducted to further examine the association of IVBP and atypical femur fractures.

Introduction

Recent studies have raised concerns that long-term treatment with oral bisphosphonate drugs may cause atypical femur fractures potentially due to impaired bone remodeling [1,2]. However, because most investigations have excluded cancer patients based on concerns for pathologic fractures [3,4], the frequency of atypical fractures in this specific population is unknown. Patients with skeletal malignancy may receive doses of intravenous bisphosphonates (IVBP) that are up to ten times greater than that used for osteoporosis [5] and represent a highly exposed and understudied population.

Current guidelines from the American Society of Clinical Oncology regarding IVBP administration for patients with breast cancer and multiple myeloma recommend 90 mg of pamidronate or 4 mg of zoledronic acid every 3–4 weeks [6,7]. For breast cancer patients with bone metastases,

Abbreviations: IVBP, Intraveneous Bisphosphonates; BC, Breast Cancer; MM, Multiple Myeloma; KPNC, Kaiser Permanente Northern California.

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continuation of IVBP is recommended until there is "evidence of substantial decline in a patient's general performance status" [7]. Patients with multiple myeloma are advised to consider IVBP discontinuation after 2 years if there is evidence of responsive or stable disease, the latter due to growing concern regarding osteonecrosis of the jaw [6]. Concerns regarding atypical femur fractures have also been raised, given the possibility of cumulative osseous microdamage from high-dose therapy [8] and the prolonged half-life of bisphosphonates for up to 10 years.

A recent study from the Memorial Sloan–Kettering Cancer Center reported 4 atypical subtrochanteric femur fractures among 327 patients who received a minimum of 24 doses of IVBP [9]. Classification was based on fracture type and radiographic criteria, including a transverse fracture pattern, cortical thickening and beaking [9]. These investigators were among the first to examine the prevalence of atypical subtrochanteric femur fractures in patients receiving high cumulative doses of IVBP. While their reported prevalence was low (1.2%), the estimates are higher than those from studies conducted in patients receiving oral bisphosphonate therapy for osteoporosis [9–11], emphasizing the need for further investigation of fracture outcomes in cancer patients. In this study, we systematically reviewed femur fracture radiographs of IVBP-exposed patients with breast cancer or multiple myeloma to identify cases of atypical femur fracture and compared the clinical features of patients with and without atypical fracture.

Methods

Kaiser Permanente of Northern California (KPNC) is a large, integrated healthcare delivery system that provides care to over three million members and represents up to one-third of insured adults across San Francisco and the greater Bay Area. Centralized databases pertaining to hospitalization discharge diagnoses, outpatient clinic diagnoses, operative and radiology reports and health plan pharmacy records have been maintained since 1995 and digital radiographic imaging since 2005. A Surveillance Epidemiology and End Results (SEER)-based Cancer Registry, pharmacy and adult oncology databases were used for initial cohort ascertainment.

Cohort identification

The source cohort included patients with metastatic breast cancer and multiple myeloma, because these two groups represent the two largest oncology populations receiving monthly infusions of pamidronate or zoledronic acid [5]. Oncology pharmacy and chemotherapy visit databases were used to ascertain the subset who received intravenous pamidronate and/or zoledronic acid and sustained nontraumatic hip or femur fractures. Patients who received IVBP for indications other than metastatic breast cancer or multiple myeloma, including osteoporosis, were excluded.

Given the potential for fracture site misclassification using administrative data [12,13], we ascertained all femur fractures (hip, femoral shaft and pathologic femur fractures) defined by principal hospital discharge diagnosis (International Classification of Diseases, Ninth Revision (ICD-9) codes 820.0X, 820.2X, 820.8X, 821.0X, 821.2X, 733.14 and 733.15), excluding ICD-9 codes for open fractures (820.1X, 820.3X, 820.9X) and fractures associated with high energy trauma (ICD-9 E800-848). None of the femur fractures occurred at or below the supracondylar metaphyseal flare (the definition used for distal femur fracture). For patients who experienced bilateral fractures, the most recent fracture was designated as the index fracture.

We initially identified 137 patients with breast cancer (BC, N = 86) or multiple myeloma (MM, N = 51) who received IVBP and sustained a femur fracture between January 2005 and December 2010 within KPNC. Based on review of pharmacy and oncology infusion records for date of initiation and cumulative number of IVBP doses, we excluded 48 patients (27 BC, 21 MM) who began IVBP therapy after the ascertained fracture, 10 patients with a history of breast cancer who received only low-dose IVBP for osteopenia/osteoporosis and 2 patients with uncertain therapy. After radiographic review, an additional 11 cases of impending fracture (6 BC, 5 MM) undergoing orthopedic repair, 2 cases of periprosthetic fracture (1 BC, 1 MM), and 2 cases without available radiographs (1 BC, 1 MM) were excluded. The final cohort consisted of 62 IVBP-treated patients (39 BC, 23 MM) who sustained femur fractures. Demographic and clinical data, including cancer history, relevant comorbidities, osteonecrosis of the jaw and other skeletal imaging (bone scintigraphy and/or osseous surveys) were obtained from health plan databases, clinical and radiology records. The study was approved by the Kaiser Foundation Research Institute's Institutional Review Board.

Fracture site verification

The anatomic site of fracture was initially categorized based on radiology, operative, and orthopedic reports as previously described [13]. All radiographs also underwent blinded review by an orthopedic trauma surgeon (CDG) for adjudication of the final fracture site: femoral neck, pertrochanteric, subtrochanteric, or femoral shaft and for identification of atypical fracture [13]. Atypical femur fractures were defined as transverse or short oblique, noncomminuted, and occurring distal to the lesser trochanter with evidence of localized periosteal reaction in the lateral cortex (beaking or flaring) and focal cortical thickening [14]. Among all fractures undergoing operative repair, we also ascertained whether intraoperative bone biopsies were sent and the biopsy findings. Fractures with biopsy-proven malignancy and fractures occurring at sites of prior radiation therapy were not considered atypical fractures.

Statistical analyses

Comparisons between subgroups were conducted using the Student's *t*-test for continuous data (Wilcoxon Mann–Whitney test for nonparametric data) and Chi-squared or Fisher exact tests for categorical data. All analyses were conducted using STATA version 10.1 (StataCorp LP, College Station, TX). A p-value of less than 0.05 was used as the criterion for statistical significance.

Results

We identified a final cohort of 62 patients (52 female, 10 male) with breast cancer (N = 39) or multiple myeloma (N = 23) who suffered a femur fracture after initiation of IVBP, after excluding patients with periprosthetic fractures (N = 2), impending fractures with prophylactic fixation (N = 11), low dose IVBP for osteoporosis/osteopenia (N = 10) or indeterminate therapy (N = 2). None had evidence of high energy trauma and none of the fractures were located in the distal femur. Table 1 summarizes the patient characteristics by cancer subtype. Patients with breast cancer were nearly all female and more likely to be white and younger at the time of fracture compared to patients with multiple myeloma. The median number of IVBP doses was 20 [interquartile range, IQR 6–41] spanning a median period of 1.9 years. Bone and/or intramedullary samples were submitted in 29 (18 BC, 11 MM) of 58 patients undergoing operative repair. Of these, 22 patients (75.9%) had biopsy samples demonstrating evidence of malignancy (15 BC, 7 MM).

Based on blinded radiographic review, ten cases (8 BC, 2 MM) were initially identified with radiographic features of an atypical femur fracture. Three of these cases (all breast cancer with 42–65 cumulative IVBP doses and subtrochanteric fracture) had intraoperative bone pathology demonstrating metastatic disease and a fourth (breast cancer, 5 IVBP doses and 8 years of oral bisphosphonate therapy for osteoporosis) had received high dose radiation treatment to the femur prior to femoral shaft fracture. These four fracture cases were not classified as atypical fracture in our case series due to evidence of bone malignancy in intraoperative samples or prior high dose radiation to the femur. It is interesting to note that among these 4 cases, two patients (one with