Cancer Therapy Associated Bone Loss: Implications for Hip Fractures in Mid-Life Women with Breast Cancer

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Abstract

Purpose: Aromatase inhibitors (AIs) have been recently associated with hip fractures. We present a case series of breast cancer survivors and a systematic review of bone health care in breast cancer.

Experimental Design: We completed clinical assessments and bone density testing (BMD) of hip fractures from January 2005 to December 2008. Prefracture and 12-month functional status was obtained. Systematic review included case reports and review of MEDLINE, PubMed, EMBASE, and Food and Drug Administration Adverse Event Reporting System (FDA AERS) from January 1998 to December 2008 (search terms: breast cancer, bone loss, osteopenia, osteoporosis, malignancy, cancer treatment, menopause, adriamycin, cytoxan, tamoxifen, and AIs).

Results: Median age was 53.5 years; five women had osteopenia, one osteoporosis. Five cases were ER (+), and received surgery, XRT chemotherapy, and anastrozole. Functional decline was noted at 12 months, with difficulty in performing heavy housekeeping, climbing stairs, and shopping. The FDA AERS database included 228 cases of fractures associated with breast cancer therapy; 77/228 (29.4%) were hip or femur fractures. Among mid-life women under the age of 64 years there were 78 fractures; 15/228 (19%) were hip and femur fractures. AIs were the most common drug class associated with fractures (n = 149, 65%).

Conclusions: Cancer treatment induced bone loss results in hip fractures among mid-life women with breast cancer. Hip fractures occur at younger ages and higher BMD than expected for patients in this age group without breast cancer. Hip fractures result in considerable functional decline. Greater awareness of this adverse drug effect is needed. Clin Cancer Res; 17(3); 560–8. ©2011 AACR.

Introduction

Hip fractures, the most serious complication of osteoporosis, usually occur in the 8th decade of life (1), and confer a 2.8-fold increased risk of dying during the following 3 months (2). Fractures contribute to deterioration in functional status (3–5). Thus, a quarter of individuals may be contributing to the occurrence of hip fractures. These drugs block estrogen production in peripheral tissues and the BMD of the 3rd generation AIs (exemestane) reduce circulating estrogen levels, leading to accelerated bone loss and an increased risk of fracture. The bone effects of AIs, like those of other serious adverse drug reactions (sADRs), are important and frequently unrecognized causes of morbidity and mortality among cancer patients. Furthermore, a median of 7 years elapses before sADRs are described by pharmaceutical suppliers or the FDA (11). Detection of sADR signals for oncology therapies is especially problematic because of the complexity in obtaining high quality reports of the clinical events associated with sADRs and difficulty in distinguishing between the underlying cancer, comorbid illness, and the toxic effect of a cancer therapy. Herein, we evaluate the occurrence of hip fractures in menopausal women with early stage breast cancer.

In clinical trials, hip fractures were rarely reported. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC)
Materials and Methods

Clinical assessment

Women with breast cancer who sustained hip fracture between the ages of 25 to 60 years were seen at the Bone Health and Osteoporosis Center at Northwestern University from January 2005 through December 2007. The protocol was approved by the Northwestern University Institutional Review Board, and patients signed informed consent. Clinical evaluation consisted of a physical exam, bone densitometry, prefracture functional assessment, and evaluation for secondary causes of bone loss (19). Evaluation at 12 months comprised physical and functional assessment.

Functional assessment

Function was measured using the 1984 validated National Health Interview Survey (NHIS): Supplement on Aging to assess functional difficulty (20–26). These 5 functional measures, or activities of daily living (ADLs), included meal preparation, heavy housekeeping, ability to climb 10 stairs, shopping, and getting out of a car. Each ADL was self reported on a 0 to 3 scale: 0 = no difficulty in performing the activity, 1 = some difficulty, 2 = much difficulty, and 3 = unable to perform the activity. Prefracture and 12-month functional status were obtained.

Assessment for secondary causes of bone loss

The majority of women with hip fractures have a secondary cause of bone loss, such as vitamin D insufficiency, calcium malabsorption, hypercalciuria, chronic kidney disease, and monochonal gammopathy of unknown significance (19). Vitamin D deficiency has been reported in high prevalence in nationally representative studies (19, 27, 28). Laboratory testing therefore included a complete blood cell count, a blood chemistry profile, serum intact PTH, 25-hydroxyvitamin D [25(OH) D] levels, serum protein electrophoresis, thyroid stimulating hormone (TSH), and results from an adequate 24-hour urine collection for calcium and creatinine. Detailed methodology has been previously published (19, 28).

Bone densitometry

Bone densitometry of the nonfractured hip and lumbar spine was performed at the Bone Health Osteoporosis Center using dual energy X-ray absorptiometry (DXA) technology (Hologic Inc.). Patients were considered to have osteoporosis if their adjusted T scores were ≤-2.5 at any measurement site. Normative databases from the Third National Health and Nutrition Examination Survey were used to determine T scores. Data from lumbar spine scans were used only if at least 2 vertebrae were visualized without interfering artifacts.

Review of National Safety databases, clinical trials, and observational databases

The FDA AERS is a pharmacovigilance database where health professionals and patients can voluntarily report sADRs. We conducted a review of the FDA’s AERS database for the years 1998 through the fourth quarter 2008. The search specified all Medical Dictionary for Drug Regulatory Affairs (MedDRA) preferred terms, including the word “fracture,” females, and an indication of breast cancer. We specifically excluded all cases with MedDRA preferred terms of osteonecrosis, which is also associated with fractures, but was not relevant to this report. Drug names were summarized from the search and included breast cancer and chemotherapeutic agents such as doxorubicin (Rubex; doxo; adriamycin; ibex; adriacin; adriblastin; caelyx, doxil, Myocet, Robanul), Cyclophosphamide (Cytoxan, Procytox; Ciclofosfamide; Cycloblastine; Cyclophosphan; Cyclostin;Endoxan; Genoxal; Genural;Neoar; Sendoxan; Syklofosfamid), and AIs such as exemestane (Aromasin), letrozole (Femara), and anastrozole (Arimidex; Pantestone). For the literature review, MEDLINE and PubMed searches for peer-reviewed articles published from 1998 to December 2008 were performed. Medical Subject Headings (MeSH) terms included: osteoporosis, bone loss, osteopenia, menopause, fractures, hip fractures, adriamycin, ciclofosfamide, doxorubicin, aromatase inhibitors exemestane (Aromasin), letrozole (Femara), and anastrozole (Arimidex; Pantestone), and tamoxifen.

Results

Six Caucasian women with hip fractures were identified in the Bone Health and Osteoporosis Center at North-
western University, with a median age of 53.5 years. Five had osteopenia (T-score <–1.0 and >–2.5), and 1 osteoporosis (T-score <–2.5). Vitamin D deficiency and low calcium absorption were identified in 2 cases (Table 1), while an additional case presented with vitamin D deficiency with high urinary calcium loss. Median age at time of diagnosis and chemotherapy induced menopause was 48 years of age. Patients had received treatment including lumpectomy, XRT and chemotherapy with cytoxan and adriamycin. Four cases were estrogen receptor positive (ER [+]) and had received AIs. Fractures occurred 1 to 4 years after cancer diagnosis.

### Functional decline
Prefracture status was independent in all activities (mean score 0) for all participants. Twelve months posthip fracture women reported clinically important functional decline with greatest difficulty in heavy housekeeping, climbing stairs and shopping (score 7 ± 1, maximum difficulty 15; refs. 20, 29). Two women reported difficulty walking more than 200 yards (P < 0.05).

### FDA Adverse events reporting system (FDA AERS)
Between January 1998 and December 2008, we identified 226 cases of fractures associated with the use of chemotherapy and/or AIs. The age distribution was uniform with an equal distribution from the age of 30 years and coincided with the age of breast cancer therapy (Fig. 1). Among women ≤64 years of age, there were 78 fractures, with 15 (19%) cases of hip and femur fractures. AIs were the most common drug class associated with fractures (n = 149, 65%) (Fig. 2).

### Observational studies
**Claims-based study.** A claims-based case control study revealed that breast cancer survivors who received anastrozole sustained more fractures after adjusting for confounding factors [odds ratio (OR): 1.21, 95% confidence interval (CI): 1.03–1.43; P = 0.02; ref. 30]. Mincey’s analysis of 12,000 patients demonstrated that the risk of bone loss remained higher in the AI group than in the non-AI group, with a 27% increase (95% CI: 4–55%; P = 0.02) and 21% (95% CI: 3–43%; P = 0.02) increase in the risk of bone loss and fractures.

**Epidemiologic studies.** Breast cancer survivors in the Women’s Health Initiative study were at increased risk for fractures [relative risk (RR): 1.31, 95% CI: 1.21–1.41] as compared to age-matched women without breast cancer (31). Likewise, hip fracture risk and fall risk increased in postmenopausal women after the diagnosis of breast cancer [hazard ratio (HR): 1.55, 95% CI: 1.13–2.11 and HR: 1.15, 95% CI: 1.06–1.25, respectively; ref. 32]. Accordingly, there appears to be a disease and non-AI cancer treatment-
related increased risk for fractures. Kanis demonstrated that the incidence of vertebral fractures in women diagnosed with breast cancer was increased (5.4% vs. 1.5%). This effect was more marked in women with a prevalent fracture at study entry (OR: 3.4). When fracture risk was adjusted for age, duration of follow-up and prevalent fracture, the risk was 4.7 (95% CI: 2.3–9.9; P < 0.0001) in women newly diagnosed with breast cancer and 22.7 (95% CI: 9.1–57.1; P < 0.0001) in the women with recurrent breast cancer (33). Higher fracture estimates are derived from European studies. In a large-scale, population-based case-control study, AIs were associated with a 2-fold increased risk for fractures (95% CI: 1.05–3.93), and a 4-fold increased risk for hip fractures specifically (95% CI: 1.03–2.09; ref. 34).

**Clinical trials.** Bisphosphonates have demonstrated consistent effects on BMD. Risedronate increases BMD in a cohort of women with breast cancer with and without prior TMX use by 2.5% ± 1.2%, (95% CI, 0.2–4.9) at the lumbar spine (P = 0.041) and 2.6% ± 1.1%, (95% CI, 0.3–4.8) at the femoral neck (P = 0.029; refs. 35–37). Alendronate, ibandronate, and clodronate had similar positive effects in women with breast cancer (38–40). More recently, the Zometa-Femara Adjuvant Synergy Z-OFAST Trial reported that hormone receptor-positive breast cancer patients receiving letrozole who received up-front versus delayed-start zoledronic acid experienced fewer fractures (5.7% vs. 6.3%), diminished disease recurrence (3% vs. 5.3%), and an increased mean BMD (6.7% vs. 5.2%; ref. 41). Similarly, the ongoing Zometa-Femara Adjuvant Synergy (ZO-FAST) trial noted that postmenopausal patients with hormone-receptor positive breast cancer receiving letrozole and immediate versus delayed zoledronic acid experienced increased mean BMD preservation (+4.39% vs. –4.9%) and a 41% relative risk reduction of disease recurrence or death (42). In summary, results of available clinical studies suggest that all 3 third-generation AIs affect bone turnover, BMD and fracture risk, and that decreased BMD, disease recurrence, and fracture risks are increased when zoledronic acid treatment is delayed.

**Clinical guidelines**

The updated 2010 American Society of Clinical Oncology (ASCO) guidelines recommend that postmenopausal women with hormone receptor-positive breast cancer consider incorporating AI therapy during adjuvant treatment. Additionally, these guidelines note that women who are either pre- or perimenopausal at the time of diagnosis should be treated with 5 years of tamoxifen. Furthermore, AI therapy should not extend beyond 5 years, and switching from an AI to tamoxifen is recommended around 2 to 3 years into treatment. Finally, ASCO guidelines advise clinicians to consider sADRs, patient preferences, and preexisting conditions when determining appropriate adjuvant endocrine therapies.

The National Comprehensive Cancer Network (NCCN) guidelines recommend that clinicians base their decisions on the results of ongoing trials. The International Society for Clinical Densitometry (ISCD) guidelines recommend BMD assessment in patients at risk for bone loss because of age (women aged ≥65 years and men aged ≥70 years), risk factors that include prior fragility fracture, medication use, or disease or medical condition that is associated with low bone mass or bone loss (43). Moreover, BMD assessments are recommended in patients for whom treatment decisions may be affected by bone health status and to monitor treatment effects in patients who are being treated for bone loss (43). Patients receiving adjuvant therapy for breast cancer typically fall into several of these categories (Table 2). AIs are associated with lower risk of thromboembolic events and endometrial cancer, but higher risk of bone loss and fractures (44). Interventions to prevent bone loss and fractures include calcium, vitamin D, and bisphosphonates. National Osteoporosis Foundation guidelines recommend treating all women with osteoporosis and those women with osteopenia who, upon FRAX® calculation (45), have a 10 year risk of fractures of 20% or 3% risk for hip fracture (46). Clinical trials with risedronate and zoledronic acid have demonstrated preservation of bone mass, although trials have not demonstrated a reduction in fracture risk due to their limited sample size (47–49).

Clinical guidelines published by Hadji and colleagues advise that all patients initiating AI therapy receive calcium and vitamin D supplements, that clinicians monitor patients who have T-scores ≥ -2.0 and no additional risk factors every 1 to 2 years to assess changes in BMD, and that patients with T-scores < -2.0 who are on AI receive bisphosphonate therapy (50). Additionally, it is recommended that bisphosphonate therapy be administered to patients receiving AIs with 2 of the following risk factors: T score < -1.5, body mass index of <20 kg/m², family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use for longer than 6 months, smoking, or are over 65 years of age. BMD should be monitored every...
2 years, and bisphosphonate therapy should be continued for at least 2 years (50).

Discussion

This case series serves to illustrate several points: hip fractures in breast cancer survivors present at an earlier age than in postmenopausal osteoporosis, result in clinically important functional decline, and occur at higher BMD than in women with postmenopausal osteoporosis.

First hip fractures in breast cancer survivors may present at an earlier age than in postmenopausal osteoporosis where hip fractures occur in the 8-decade of life (mean age 74 years). Notably, breast cancer survivors can present with hip fractures as early as the sixth decade of life.

Second, hip fractures are associated with functional decline among middle-aged breast cancer patients. Greater awareness of the functional and quality of life impact of CTIBL fracture complications in cancer survivors is necessary. Hip fractures in older women account for considerable functional impairment, morbidity, hospitalizations, and increased mortality (7–10). Osteoporotic fractures such as wrist, vertebral and hip fractures are associated with functional decline (51–54). The functional impact of osteoporotic fractures include a 1.7- to 3.0-fold increase in difficulty bending, lifting, reaching, walking, climbing stairs, and descending stairs and are significantly associated with 1.9 to 6.7 times more difficulty in dressing, cooking, shopping, and performing heavy housework. Hip fractures are more strongly associated with difficulty walking and descending stairs, whereas spine fractures demonstrated a stronger association with difficulty bending, and lifting (54). To date, there is a paucity of pharmacovigilance studies that assess the safety of chemotherapy and adjuvant therapy in early stage breast cancer patients.
Third, it would appear that most of the hip fractures reported occurred in women with osteopenia. Hence, this group of women is not currently recommended to receive osteoporosis therapy per ASCO clinical guidelines. No specific osteoporosis therapy is advocated (55), as bone health guidelines state "Breast cancer patients found to have osteopenia based on BMD results (T-score between ≤1 and ≤ -2.5) should have their therapy individualized, but current evidence cannot support routine intervention with bisphosphonates for this group" (55). This raises concern that the intervention threshold may exclude women with osteopenia at high-risk for fractures. Within the FDA AERS database, 102 (44.7%) reports documented concomitant use of bisphosphonates. The most common bisphosphonate was zoledronic acid (n = 44, 19.3%).

Fourth, safety warnings in the Arimidex package insert report the most common side effects (>10%) seen in ATAC were osteoporosis and fractures (56). The Letrozole (Femara) and Exemestane package inserts, however, only describe bone loss (57, 58). The European Medicine Agency notes that Anastrozole was approved in 1995 in the United Kingdom. The safety profile was considered to be well established. Moreover, no product-specific pharmacovigilance issues or pre- or postauthorizations that were not adequately covered by the product label were identified (59). In 2006, the European Drug Watch reported that anastrozole was the only drug with mature safety and tolerability data, and that the drug presented a favorable risk-benefit profile compared to tamoxifen for a full 5-year treatment period (60). Although aromatase inhibitors are associated with increased risk of osteoporotic fracture, bone problems with AIs are considered to be both predictable and manageable (61). In Germany, the Portal fur Medicine and Gesundheit noted in 2006 that women with a normal BMD who received a 5-year course of treatment with anastrozole would not be at risk of developing osteoporosis. These researchers found that the rate of bone fracture among women taking anastrozole was comparable to the normal patient population of that age group contrasting with the work of other researchers (34, 62). In 2004, Canada Health approved the use of anastrozole with certain conditions, namely bone loss, fractures and hyperlipidemia (63).

Fifth, drug-induced osteoporosis as seen with chronic glucocorticoid treatment has been associated with rapid and significant bone loss characterized by osteocyte and osteoblast apoptosis and a major loss of trabecular connectivity (64–66); thus, an increased vertebral fracture risk occurs at higher BMD thresholds in glucocorticoid-induced osteoporosis (67). The characteristics of architectural changes induced by chemotherapy and AIs are yet to be determined. Studies corroborate fracture occurrence with T-score > -2.5 in the setting of abnormal bone architecture (68). In the Rotterdam study, nonvertebral fractures occurred in 56% and 79% of women and men, with a T-score above ≥ -2.5 (69). In the Study of Osteoporotic Fractures, 54% of patients with nonvertebral fracture had a baseline central T-score ≥ -2.0 (68). Trabecular bone is composed of interconnected vertical and horizontal struts, which impart its compressive strength. In osteoporotic bone, trabeculae are thinner, less abundant, and spaced at greater distances, which greatly reduces structural integrity (70). Deterioration in bone microarchitecture is associated with increased vertebral fracture risk (71). Analysis of bone biopsies in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial showed greater disruption of the trabecular lattice per area and trabecular bone pattern factor in women with vertebral fractures than in those without (72). In an analysis of individuals with and without vertebral fractures (71), there was significantly greater deterioration in bone microarchitecture in the group with vertebral fracture (71).

Of the more than 200,000 cases of breast cancer in the United States each year, 25% occur before menopause (73). In these women, chemotherapy induced menopause (74), ovarian ablation (75, 76), and hormone therapy all contribute to accelerated bone loss (77). The consequences of hip fractures are sizable, including hospitalizations (78), and need for long term care (79). Vertebral fractures may lead to hospitalization (80), with recurrent vertebral fractures often resulting in impairment in pulmonary function and predisposing affected individuals to respiratory infections (78, 81, 82). Fracture of the wrist may be less severe, but they can impair the ability to cook or clean. Therefore, although chemotherapy and adjuvant therapy prolong disease-free survival for patients with breast carcinoma (74), these therapies can induce long-term side effects, such as functionally disabling osteoporotic fractures.

Given the association between functional impairment with distinct skeletal sites, there is concern that the functional impact of fractures may be underestimated in current cancer clinical trials. The latest version of the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03, 2010) lists fractures according to specific skeletal site, including hip, spinal, and wrist fractures. As noted from this literature review, many of the consequences of fractures depend on the skeletal site, thus this recent modification of the adverse event of fractures with fracture site identification allows for more comprehensive adverse event reporting (83).

The third-generation AIs are now an important adjuvant option for the treatment of estrogen positive early breast cancer, and are recommended as the preferred therapy by clinical guidelines: ASCO, the NCCN, and the St. Gallen International Expert Consensus (84–86). The cost effectiveness of Anastrozole and other AIs have been well documented (87–91). As the number of cancer survivors increase, survivorship issues become more pressing. In 2005, the Institute of Medicine report highlighted shortfalls in the clinical care provided to the more than 10 million cancer survivors in the United States, with breast cancer accounting for more than 22% of cases (92). Young and middle-aged women are more likely to receive toxic multimodal treatments that contribute to ovarian failure and early menopause, putting this group of women at high risk.
for CTIBL, osteoporosis, fractures, and years of productive life lost. Reducing this risk is critical as young survivors have the greatest longevity. Available clinical guidelines for management of CTIBL set intervention thresholds too low for effective prevention in many women with CTIBL. Bisphosphonates have demonstrated effective prevention of bone loss associated with ovarian ablation and AIs use (48, 93).

Limitations to this study include the low data quality regarding completeness and accuracy of FDA AERS reports, as these reports have limited clinical and basic science data. Additionally, data in these reports are de-identified, which further limits case identification and ability to eliminate redundancy.

Although the outcome for early stage breast cancer is excellent, the occurrence of CTIBL and its resulting complications such as hip fractures, raise concern about the long-term benefits to breast cancer survivors. It is imperative that future studies assess the efficacy of current intervention thresholds for bone health management in breast cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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