High prevalence of vertebral fractures in women with breast cancer starting aromatase inhibitor therapy

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Background: The purpose of this study was to describe bone status in a large cohort of postmenopausal women with nonmetastatic breast cancer, at the initiation of aromatase inhibitor therapy.

Patients and methods: A prospective, transversal and clinical study was conducted. Each woman had an extensive medical history, a biological evaluation, a bone mineral density (BMD) measurement and spinal X-rays.

Results: Four hundred and ninety-seven women aged 63.8 ± 9.6 years were included in this study. Eighty-five percent of these women had a 25-OH vitamin D concentration < 75 nmol/l. One hundred and fifty-six women (31.4%) had a T-score < 2.5 at one of the three site measurements. Ninety-five women (19.1%) had a history of nonvertebral fracture with a total of 120 fractures. Spine X-rays evaluation revealed that 20% of the women had at least one vertebral fracture. The presence of vertebral fracture was associated with nonvertebral fracture history [odds ratio (OR) 1.6, 95% confidence interval (CI) 1.1–2.4] and with spine BMD (OR 1.4, 95% CI 1.1–1.7). The prevalence of vertebral fracture reached 62.9% in women with age above 70 years and femoral T-score < −2.5.

Conclusion: Before starting aromatase inhibitor therapy for breast cancer, a large proportion of women had a vitamin D insufficiency and vertebral fractures.

Key words: aromatase inhibitor, breast cancer, osteoporosis, vertebral fracture, 25-hydroxyvitamin D

Introduction

Breast cancer is the most frequent malignancy in women in Europe and in North America [1, 2]. Adjuvant aromatase inhibitor therapy has been shown to reduce breast cancer recurrence by ∼50% when compared with tamoxifen [3–5]. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study including 9366 postmenopausal women with a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival, time-to-recurrence and reduced distant metastases and contralateral breast cancers [3]. Anastrozole and letrozole are nonsteroidal reversible aromatase inhibitors and exemestane is an irreversible steroid inactivator of the aromatase enzyme [6]. These three drugs inhibit the aromatization of androgens and their conversion to estrogens in peripheral tissues by blocking the P450 cytochrome enzyme aromatase [6]. The substantial reduction in estrogen concentrations can lead to bone loss and aromatase inhibitor therapy has been associated with a decrease in bone mineral density (BMD) and an increased fracture risk [7–10]. In the ATAC study, after a median follow-up of 68 months, clinical fractures were significantly more frequent in the anastrozole group than in the tamoxifen group (11.0% versus 7.7%, respectively), with particularly increased risk of vertebral fractures [7]. In the same way, the Breast International group 1-98 study compared letrozole and tamoxifen in 8028 postmenopausal women [10]. At a median follow-up of 60.3 months, the clinical fracture incidence was significantly higher in the letrozole group compared with the tamoxifen group (9.3% versus 6.5%).

These studies also suggest that aromatase inhibitors-induced bone loss and fracture incidence depend on initial bone status so do BMD and prevalent fractures. Before starting aromatase inhibitor therapy, the individual bone status of women with breast cancer is particularly variable. Several factors including age, body mass index (BMI), age at onset of menopause, prevalent fractures, previous use of chemotherapy or corticosteroids, 25-hydroxyvitamin D plasma level can account for this bone status heterogeneity. The aim of this prospective, transversal and clinical study was to describe BMD, vertebral and nonvertebral fractures and biologic parameters, in a large cohort of women with nonmetastatic breast cancer, at the initiation of aromatase inhibitor therapy.

Patients and methods

Patients

This prospective study was conducted by both the oncology center (Paul Papin Cancer Institute, ICO) and the Department of rheumatology of the University Hospital of Angers.
University Hospital of Angers. Between January 2006 and January 2009, 920 women with breast cancer were examined in the oncology center. Among them, 615 women with a tumor expressing estrogen receptor were treated by aromatase inhibitor therapy. Finally, 530 women without bone or soft tissue metastasis agreed to have an osteoporosis assessment within the first 3 months of aromatase inhibitor therapy and 497 women without bone medication were included in this study (see the flow chart Figure 1).

**methods**

**clinical parameters.** An extensive medical history and a physical examination were obtained for each subject including age, age at onset of menopause, family history of osteoporosis, personal history of fractures, medications, treatment of cancer (radiotherapy, chemotherapy, tamoxifen), alcohol and tobacco use, physical activity and calcium food intake.

**biological parameters.** Fasting serum samples were assayed for calcium, phosphate, albumine, creatinine, 25-hydroxy vitamin D (Nichols Institute Diagnostics, San Clemente, CA) and 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (PTH) (Beckman Coulter, Brea, CA), bone formation markers (osteocalcin and bone alkaline phosphatase) and bone resorption marker (C-telopeptide).

**bone mineral densitometry.** BMD was measured using dual energy X-ray absorptiometry (DXA) operating in fan-beam mode (Hologic QDR 4500A densitometer; Hologic Inc., Waltham, MA). Quality control scans were carried out daily, using the manufacturer-supplied anthropomorphometric spine phantom; the long-term (>1 year) coefficient of variation was 0.40%. Lumbar BMD was assessed from L2 to L4, in the posteroanterior view incidence and fractured vertebrae were excluded from analysis. Total hip BMD was measured at upper left femur. The mean precision error of DXA measurement is <1.5% for the lumbar spine and <2% for hip BMD. As usually, the results were expressed in absolute values (g/cm²) and using the T-score [Standard deviation (SD)]. The T-scores were calculated using manufacturer’ references and expressed the difference between the subject value and mean value of healthy young women. The World Health Organization has defined normal BMD as a T-score above −1 in the lumbar spine and total hip, low bone density as a T-score between −1 and −2.5, osteoporosis as a T-score < −2.5.

**radiographic assessment.** Anteroposterior and lateral spinal X-ray films were taken at the time of the DXA. They were analyzed independently by two trained investigators (at least 10 years experience in rheumatology and bone diseases) who were unaware of the patient BMD. A patient was classified as having a vertebral fracture if both readers independently found a definite fracture. He was classified as normal if both readers independently found that the films were normal. When the readers disagreed, the films were reviewed in conference by both investigators. The semiquantitative method described by Genant was used to define vertebral fractures with three severity grades. Grade 1 represents a mild fracture, with 20%–25% reduction in vertebral body height. Grade 2 corresponds to a moderate fracture, with 25%–40% reduction in vertebral height. Grade 3 corresponds to a severe fracture, with at least 40% reduction in vertebral height [11].

**statistical analysis**

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS release 15.0; SPSS Inc., Chicago, IL). All results are expressed as the mean ± 1 SD. The nominal significance level was set at 0.05. The relationships between biological parameters were analyzed using multivariate model including age and BMI. Comparisons between women with vitamin D severe deficiency and women with optimal vitamin D level were tested by the Student’s t-test. The associations of clinical or biological parameters and vertebral or nonvertebral fractures were explored using logistic regression analysis. Backwards stepwise algorithms were used to arrive at the best model. Variables were included in the final model if the P value was <0.05.
results

clinical characteristics

The women’s characteristics are presented in Table 1. Briefly, the mean age was 63.8 ± 9.6 years; the mean age at onset of menopause was 49.4 ± 4.5 years. Breast cancer was previously treated by surgery in 97% of women, by radiotherapy in 96.4% of women and by chemotherapy in 58.4% of women. Furthermore, 40.2% of women had been previously treated by tamoxifen for a mean duration of 34.2 months. Aromatase inhibitor therapy prescribed was anastrozole in 68.4% of women, exemestane in 19.3% and letrozole in 11.7%.

biological results

The mean plasma level of 25(OH)D was 46.2 ± 23 nmol/l. Fifty-eight women (11.7%) had a 25(OH)D concentration <25 nmol/l (severe deficiency), while 366 women had a 25(OH)D concentration between 25 and 75 nmol/l. Only 73 patients (14.7%) had an optimal concentration between 25 and 75 nmol/l. The mean PTH level was 34.7 ± 18.9 pg/ml. Five patients had primary hyperparathyroidism with serum calcium >2.6 mmol/l and increased PTH. In accordance with the high prevalence of vitamin D deficiency, 17.2% of women had secondary hyperparathyroidism with normocalcemia and PTH >50 pg/ml [12].

Multivariate analysis showed that 25(OH)D level was inversely correlated with age (r = -0.25, P < 0.001), BMI (r = -0.25, P < 0.001), PTH (r = -0.17, P < 0.001). After 74 years, 25.7% of women had a severe deficiency (25-hydroxy vitamin D level <25 nmol/l) [13] and 93.2% had a concentration <75 nmol/l. Furthermore, 11.1% of patients with BMI above 30 kg/m² had a severe deficiency and 97.0% had a concentration <75 nmol/l.

Compared with women with optimal vitamin D levels, women with severe deficiency were older (68.5 versus 59.9 years, P < 0.001), had a higher BMI (27.5 versus 24.3 kg/m², P < 0.001), were smaller (154.9 versus 159.4 cm, P < 0.001), had a higher PTH level (36.4 versus 28.4 pg/ml, P < 0.01) and a higher prevalence of vertebral fractures (25.8% versus 12.1%, P = 0.05).

Table 1. Clinical characteristics of 497 patients with breast cancer starting aromatase inhibitor therapy (mean ± SD)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Mean</th>
<th>SD</th>
</tr>
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<tbody>
<tr>
<td>(n = 497)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Age at breast cancer diagnosis (years)</td>
<td>60.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Age at onset of the menopause (years)</td>
<td>49.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Parity</td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.4</td>
<td>13.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Tobacco use (%)</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Drinking at least one alcoholic glass per day (%)</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>470</td>
<td>130</td>
</tr>
<tr>
<td>Walking (h/week)</td>
<td>2.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Bone mineral densitometry

The results of BMD assessment are presented in Table 2. Respectively, 40.4%, 43.5% and 44.7% of women had a low BMD (T-score < -1) at lumbar spine, femoral neck and total hip. In addition, 24.5%, 14.0% and 13.7% of women had a T-score < -2 at lumbar spine, femoral neck and total hip, respectively. Finally, 156 women (31.4%) had a T-score < -2 at one of the three sites (lumbar spine or femoral neck or total hip).

Logistic regression analysis showed that lumbar spine BMD was negatively associated with age [odds ratio (OR) per decade 2.3, 95% confidence interval (CI) 1.5–2.6] and positively associated with BMI (OR per kg/m² 1.2, 95% CI 1.1–1.3). The same results were observed for hip BMD, which was negatively associated with age and positively associated with BMI. By contrast, previous use of tamoxifen or chemotherapy was not associated with spine or hip BMD.

prevalent fractures

nonvertebral fractures. Medical assessment showed that 95 women (19.1%) had a history of nonvertebral fracture with a total of 120 fractures concerning the wrist (N = 40), the ankle (N = 19), the ribs (N = 12), the hip (N = 11), the humerus (N = 9) and other sites (N = 30). Logistic regression analysis showed that the presence of nonvertebral fracture was associated with age (OR per decade 1.3, 95% CI 1.1–1.8), with the decrease in lumbar spine BMD (OR 1.6, 95% CI 1.3–2.0) and the decrease in femoral BMD (OR 2.0, 95% CI 1.5–2.5). By contrast, no association was observed between nonvertebral fracture and tamoxifen or chemotherapy use.

vertebral fractures. The results of spine X-ray analysis are presented in Table 3. At least, one osteoporotic vertebral fracture was observed in 98 women (19.7%). Seventy-two women (14.5%) had one vertebral fracture and 26 women (5.2%) had multiple vertebral fractures, without history of trauma. These fractures were clearly osteoporotic without osteolysis. Logistic regression analysis showed that the presence of vertebral fracture was associated with age (OR per decade 1.5, 95% CI 1.2–2), with nonvertebral fracture history (OR 1.6, 95% CI 1.1–2.4), with the decrease lumbar spine BMD (OR 1.4, 95% CI 1.1–1.7) and the decrease femoral BMD (OR 1.5, 95% CI 1.2–2). In other words, 10.1% of women younger than 60 years, 18.4% of women between 60 and 70 years and 32.8% of women after 70 years had vertebral fracture. In addition, 9.9%...
of women with normal lumbar BMD (T-score > -1), 20.9% of women with low lumbar BMD (-2 < T-score < -1) and 31.5% of women with lumbar T-score < -2 had at least one vertebral fracture. Finally, the prevalence of vertebral fracture reached 62.9% in women aged >70 years with femoral T-score < -2.5. By contrast, no association was observed between vertebral fracture and tamoxifen use, chemotherapy use, family history of fractures, BMI, calcium intake and age at onset of menopause.

**discussion**

Several studies have underlined the negative bone impact of aromatase inhibitor therapy in women with breast cancer. Furthermore, it has been shown that the severity of drug-induced osteoporosis (e.g. steroids, antiestrogens, antiandrogens) depended on gender, age, baseline BMD and prevalent fractures [7]. The aim of our prospective study was to evaluate the bone status of a large cohort of 497 postmenopausal women with breast cancer before aromatase inhibitor therapy. To better describe the bone status, this prospective evaluation was carried out within 3 months of aromatase inhibitor therapy initiation and included bone biology, spine and hip BMD measurements but also systematic thoracic and lumbar spine X-rays, which is the reliable way to diagnose asymptomatic vertebral fractures and thus evaluate osteoporosis severity.

Hypercalcemia has been discovered in 1% of women of this cohort in relation with primary hyperparathyroidism and not to bone metastasis. This result was not surprising considering the prevalence of primary hyperparathyroidism in general women population after 60 years [14]. However, it indicates that discovery of hypercalcemia should not be systematically related to cancer.

*In vitro* studies have shown that vitamin D receptor is expressed on normal and malignant breast cells. Furthermore, the 1-α-hydroxylase is expressed in breast tissue, allowing local activation of the predominant circulating form of vitamin D to active 1,25(OH)2 vitamin D3 [15]. Experimental studies have shown that 1,25(OH)2 vitamin D3 inhibits the proliferation of breast cancer cell line, promotes differentiation and induces apoptosis. Ecologic studies have shown a relationship between latitude of residence and breast cancer risk and some cross-sectional studies have shown an inverse association between vitamin D intake and breast density. Despite conflictual results between intervention studies [16, 17], low vitamin D levels have been associated with increased breast cancer mortality [18]. The main biological result of this study was that 85% of women had a nonoptimal 25(OH)D level (<75 nmol/l) and that severe deficiency (<25 nmol/l) was present in nearly 12% of women. The plasma level of 25(OH)D was negatively correlated with age and BMI. Confavreux et al. [19] observed similar results in a smaller cohort of 118 women with a mean 25-hydroxy vitamin D level measured of 51.5 nmol/l. In 147 women suffering from breast cancer, Geisler et al. [20] found that 88% of patients had 25(OH)D concentration <75 nmol/l. In our study, due to vitamin D insufficiency 17% of women had secondary hyperparathyroidism, which has been largely associated with excessive bone loss and fracture [21]. Our large cohort of nearly 500 women led us to describe some particular subgroups of patients. Thus, women with BMI >30 kg/m2 were the group most concerned by vitamin D insufficiency with 97% of women less than the threshold of 75 nmol/l. The higher prevalence of severe deficiency was observed in older women (age >74 years). The prevalence of vertebral fracture reached 25% in women with severe deficiency and after adjusting for age, their fracture risk was twofold increased compared with women with optimal levels of vitamin D.

Obesity and late onset of menopause are classical risk factors for breast cancer but are usually described as protective factors against osteoporosis. Therefore, in this cohort, it was interesting to observe that nearly 50% of women had a low BMD (T-score < -1), and that 30% of women had a T-score < -2, a value which is considered by many groups as a therapeutic intervention threshold to prevent osteoporotic fractures in case of introduction of an aromatase inhibitor [22–24]. In a retrospective study, Chen et al. [25] showed similar results with 27.2% of women with breast cancer and T-score < -2.5. In our study, spine and hip BMD was negatively correlated with age and positively associated with BMI. Despite these classical relationships, 20% of women with BMI > 25 kg/m2 and 21.2% of younger women (<60 years) had a T-score < -2. First, these results suggest that a large proportion of women with breast cancer have low BMD before starting aromatase inhibitor therapy. Second, they underline that BMD measurement should be systematically proposed, despite young age or high BMI.

Epidemiologic studies have strongly demonstrated that most wrist, hip, humeral and vertebral fractures are a consequence of postmenopausal bone loss and osteoporosis [26, 27]. Particularly, the age-standardized population prevalence of vertebral fracture is estimated ~12% between 50 and 79 years [28]. In the last 10 years, several groups have shown that two-thirds of vertebral fractures are asymptomatic and only detected by X-rays. The presence of vertebral fracture is strongly associated with new fracture occurrence, height loss, kyphosis, chronic pain, analgesic use, decrease in quality of life, and...
moribidity and mortality [29, 30]. Bluc et al. [31] showed that age-adjusted Standard Mortality Rates (SMRs) are increased following vertebral fractures in women (SMRs 1.82) and persist for 5 years. In our study, nearly 20% of women had at least one osteoporotic vertebral fracture and 5% had multiple fractures. Previous retrospective studies without X-ray examination have shown a lower vertebral fracture prevalence of ~10% [32, 33]. In our study, the fracture discovery was facilitated by the systematic realization of X-rays and their evaluation by two trained investigators, which allowed us to look for asymptomatic fractures. As expected, the presence of vertebral fracture was negatively associated with age and low BMD. The prevalence reached 62.9% in older women with very low BMD. However, a significant proportion of fractures was detected in young women with T-score > −2. This specific feature was observed in other secondary osteoporosis, such as corticosteroid-induced osteoporosis [34]. On the one hand, this result indicates that not only BMD but also bone quality factors, such as trabecular bone connectivity, bone remodeling or collagen properties, play a key role in the pathogenesis of these vertebral fractures [35]. On the other hand, from a clinical point of view, our results strongly suggest that both BMD measurement and X-ray assessment are useful to evaluate bone status and fracture risk in women with breast cancer. These vertebral fractures were associated with nonvertebral fracture history including wrist, ankle, ribs, hip and humeral fractures. The strong relationship between the presence of these fractures and BMD (with a relative risk of 1.6 for spine and 2.0 for hip density) indicates that these fractures belong to the spectrum of osteoporosis.

In conclusion, our study shows that before starting aromatase inhibitor therapy for breast cancer, 85% of women had a nonoptimal 25(OH)1D level, 30% had a low bone mass, 20% had vertebral fractures and 19% had a history of nonvertebral fracture. These results strongly suggest that bone biology, spine and hip BMD measurements but also systematic spine X-rays are useful in these women to accurately evaluate bone status and propose vitamin D supplements and specific therapy to prevent antiaromatase-induced osteoporosis.

disclosure

The authors declare no conflict of interest.

references