Fracture incidence after 3 years of aromatase inhibitor therapy

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Background: The purpose of this study was to describe the fracture incidence and bone mineral density (BMD) evolution in a large cohort of post-menopausal women with breast cancer after 3 years of aromatase inhibitor (AI) therapy.

Patients and methods: A prospective, longitudinal study in real-life setting. Each woman had an extensive medical assessment, a biological evaluation, a BMD measurement, and systematic spinal X-rays at baseline and after 3 years of AI therapy. Women with osteoporosis at baseline (T-score < −2.5 and/or non-traumatic fracture history) were treated by oral weekly bisphosphonates.

Results: Among 497 women (mean age 63.8 ± 9.6 years) included in this study, 389 had a bone evaluation both at baseline and after 3 years of AI therapy: 267 women (mean age 61.2 ± 8.6) with no osteoporosis at baseline and 122 women (mean age 67.2 ± 9.1) with osteoporosis at baseline justifying a weekly oral bisphosphonate treatment. Women without bisphosphonates had a significant decrease in spine BMD (−3.5%, P < 0.01), neck BMD (−2.0%, P < 0.01), and total hip BMD (−2.1%, P < 0.01) over the 3 years but only 15 of them (5.6%) presented an incident vertebral or non-vertebral fracture. In osteoporotic women treated with bisphosphonates, spine and hip BMD were maintained at 3 years but 12 of them (9.8%) had an incident fracture. These fractured women were significantly older (74.1 ± 9.8 versus 66.5 ± 8.8) but also presented BMD loss during treatment suggesting poor adherence to bisphosphonate treatment.

Conclusion: This real-life study confirmed that AIs induced moderate bone loss and low fracture incidence in post-menopausal women without initial osteoporosis. In women with baseline osteoporosis and AI therapy, oral bisphosphonates maintain BMD but were associated with a persistent fracture risk, particularly in older women.

Key words: aromatase inhibitor, breast cancer, osteoporosis, vertebral fracture, bisphosphonate

introduction

Histopathologic studies have shown that ~80% of breast cancer expresses the estrogen receptor (ER+). In post-menopausal women, the estrogen stimulation of breast cancer can be suppressed by targeting the ER either directly by selective ER modulators such as tamoxifen or indirectly by blocking the aromatization of androgens and their conversion to estrogens in peripheral tissues using aromatase inhibitors (AIs). The current AI third generation, letrozole, anastrozole, and exemestane, has become the standard of care for the adjuvant endocrine treatment of ER+ breast cancer, either as initial therapy or as sequenced treatment after 2–3 years of tamoxifen [1]. The substantial reduction in estrogen concentrations induced by AIs is associated with increased bone turnover and leads to a decreased bone mineral density (BMD) and an increased risk of fracture [2, 3]. Thus, it is now largely recommended that all women starting AI therapy should be carefully assessed for their baseline risk of osteoporotic fractures including a full evaluation of all clinical risk factors, a dual energy X-ray absorptiometry (DXA) examination [4] and spinal X-rays to provide thorough information on symptomatic or to diagnose asymptomatic vertebral fractures which occur in ~20% of women [5]. Randomized control studies have shown the efficacy of antiresorptive treatments, bisphosphonate or denosumab, in preventing bone loss in post-menopausal women with breast cancer receiving AIs [6–9]. However, few data exist concerning the effects of oral bisphosphonate on fracture occurrence in women with severe osteoporosis at baseline, and the etiologies of failure of bisphosphonates in this population. Furthermore, the vertebral and non-vertebral fracture incidence induced by AI therapy in women without osteoporosis treatment has not been studied much. The primary objective of this 3-year prospective and longitudinal real-life study was to describe fracture incidence and particularly vertebral fractures...
incidence in women with or without osteoporosis at baseline receiving AI therapy. The second objective was to measure the evolution of their lumbar spine and hip BMD.

patients and methods

patients

This 3-year prospective and longitudinal study was conducted by both the Department of Medical Oncology and the Department of Rheumatology of the University Hospital of Angers between January 2006 and January 2009. Four hundred and ninety-seven women with ER+ breast cancer had an osteoporosis assessment within the first 3 months of AI therapy. Calcium and vitamin D were prescribed if necessary with dosages adapted to their baseline levels. Women with osteoporosis at baseline, characterized by a T-score $<-2.5$ and/or osteoporotic (non-traumatic) fracture history, were proposed to take a weekly oral bisphosphonate treatment, risedronate 35 mg or alendronate 70 mg, and constituted the AI + B group. The other women, without osteoporosis at baseline, constituted the AI group. Women were invited to have a second bone status assessment after 3 years of AI therapy according to the same protocol as the first one.

bone evaluation

The bone evaluation, which included clinical examination, biological tests, BMD measurements, and spine X-rays has been described previously [5]. Briefly, all included women had an extensive medical history assessment and a physical examination. A fasting serum sample was carried out to measure calcium, phosphate, albumin, creatinine, 25-hydroxy vitamin D, parathyroid hormone (PTH), bone formation markers (osteocalcin and bone alkaline phosphatase), and bone resorption marker C-telopeptide (CTX). BMD was measured by the same technician and the same machine using DXA (Hologic® QDR 4500A densitometer, Hologic Inc., Waltham, MA, USA) at lumbar spine, total hip, and neck. Lumbar and dorsal spinal antero-posterior and lateral X-ray films were taken at the time of the DXA. They were analyzed independently by two trained investigators who were unaware of the patient BMD. A patient was classified as having a vertebral fracture if both readers independently found a definite fracture. When the readers disagreed, the films were reviewed in conference by both investigators. Finally, X-ray films obtained at baseline and at 3 years were compared in order to look for new vertebral fractures.

statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS release 15.0, Spss Inc., Chicago). All results were expressed as the mean ± 1 standard deviation. The nominal significance level was set at 0.05. The evolution of BMD and bone markers before and after 3 years of AIs therapy was measured by the Student’s t-test for paired samples. In each group, comparisons among fractured and non-fractured women were tested using the Mann–Whitney test.

results

Baseline patient characteristics were presented in a previous paper [5]. Briefly, the mean age at the time of the evaluation was 63.8 ± 9.6 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. 40.2% of women received initially tamoxifen as adjuvant hormonotherapy for a mean duration of 34.2 ± 19.4 months. AI therapy prescribed was anastrozole in 68.4% of women, exemestane in 19.3%, and letrozole in 11.7%. Respectively, 14.1, 7.1, and 5.8% of women had a T-score of $<-2.5$, at lumbar spine, femoral neck, and total hip. A history of non-vertebral fracture concerned 95 women (19.1%), 72 women (14.5%) had one vertebral fracture and 26 women (5.2%) had multiple vertebral fractures without any history of trauma. As indicated in the flow chart, 389 (78.3%) women had a second evaluation after 3 years of AI therapy (Figure 1).

![Flow chart](image-url)
Among them, 267 women did not have osteoporosis at baseline and therefore did not have any bisphosphonate treatment (AI group) and 122 women with osteoporosis at baseline were advised to take bisphosphonate (AI + B group). Because these 389 women were different for bone status and treatment, both groups were analyzed separately (Table 1).

### women without osteoporosis at baseline (AI group)

Two hundred and sixty-seven women (mean age 61.2 ± 8.6 years) were included in this group. These women had a significant decrease in spine BMD (0.984 ± 0.117 versus 0.948 ± 0.128 g/cm²; −3.5%, *P* < 0.01), neck BMD (0.740 ± 0.096 versus 0.725 ± 0.104 g/cm²; −2.0%, *P* < 0.01), and total hip BMD (0.904 ± 0.124 versus 0.885 ± 0.125 g/cm²; −2.1%, *P* < 0.01) after 3 years of AI treatment and 15 of them (5.6%) with a baseline T-score of <−2.5 became osteoporotic (T-score < −2.5). Decreased bone loss at lumbar spine over 3 years was only significant in women ≤65 years (−0.041 g/cm², *P* = 0.001), while the bone loss was lower and non-significant in women >65 years (−0.023 g/cm²; *P* = 0.3). In contrast, there was no significant difference concerning bone loss at total hip and femoral neck in the women above and below 65 years. There was no statistical difference in bone loss at the three sites among women with normal T-score of >−1 and those with T-score comprised between −1 and −2.5. History of the primary use of tamoxifen did not have any impact on the mean bone loss. The mean 25 OH vitamin D concentration significantly increased from 47.2 to 63.1 nmol/l (*P* < 0.01) and the sCTX level significantly decreased by 12.5% (*P* < 0.01) over the 3 years. Over the 3 years, 15 women (5.6%) presented at least one new osteoporotic fracture, for a total of 24 fractures. Among them, 15 non-vertebral fractures (three hips, four wrists, two ribs, two ankles, one humerus, one elbow, one pelvis, and one patella) and 9 vertebral fractures (confirmed by spinal X-rays) were observed. Among the 15 patients with incident fracture, only one had a baseline T-score of <−2.5. Only spine BMD (0.893 ± 0.0594 versus 0.898 ± 0.117 g/cm², *P* = 0.001) was significantly lower at baseline in women who had incident fractures (supplementary data S1, available at Annals of Oncology online). History of the primary use of tamoxifen did not have any impact on the fracture incidence. Finally, we did not observe any significant difference in BMD loss over the 3 years among the women with and without new fractures.

### women with osteoporosis at baseline (AI + B group)

One hundred and twenty-two women (mean age 67.2 ± 9.1 years) were included in this group. No significant change in spine BMD (0.800 ± 0.107 versus 0.804 ± 0.128 g/cm²; *P* = 0.7), neck BMD (0.625 ± 0.087 versus 0.626 ± 0.091 g/cm², *P* = 0.5), and total hip BMD (0.753 ± 0.103 versus 0.751 ± 0.108 g/cm², *P* = 0.3) was observed during the follow-up. History of the primary use of tamoxifen did not have any impact on the mean bone loss. The mean 25 OH vitamin D concentration significantly increased from 47.5 to 74 nmol/l (*P* < 0.01) and sCTX significantly decreased by 42% (*P* < 0.01). Over the 3 years, 12 women (9.8%) presented at least one new osteoporotic fracture for a total of 17 fractures. Among them, 10 non-vertebral fractures (four wrists, two hips, two ankles, one humerus, and one collarbone) and 7 vertebral fractures confirmed by spinal X-rays occurred. Women with incident fracture were significantly older at baseline than women without fracture (74.1 ± 9.8 versus 66.5 ± 8.8; *P* = 0.01) (supplementary data S2, available at Annals of Oncology online). History of the primary use of tamoxifen did not have any impact on the fracture incidence. Women with incident fracture had a decreased BMD at lumbar spine (−8%), neck (−6.1%), and total hip (−5.7%) at the third year compared with baseline data but because of the small number of fractures, these results were not significant (Figure 2). In the same way, the decrease in CTX was marginal in these women with new fractures (Figure 2). No serious effect associated with the use of bisphosphonates has been recorded during the follow-up of the study notably no osteonecrosis of the jaw.

### discussion

This original study evaluated the fracture incidence and the BMD evolution in post-menopausal women with breast cancer treated by AIs. Because vertebral fracture is the main osteoporosis complication before 75 years, the evaluation systematically included spinal X-rays. The main result of this study was the limited impact of AIs on bone in women without osteoporosis at baseline. These women had a moderate BMD decrease at the three sites over the 3 years, with a higher decrease in spine BMD.

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**Table 1.** Baseline characteristics of 389 patients with breast cancer (mean ± SD) according to their bone status

<table>
<thead>
<tr>
<th></th>
<th>AI group (N = 267)</th>
<th>AI + B group (N = 122)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.2 ± 8.6</td>
<td>67.2 ± 9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 5.8</td>
<td>25.7 ± 4.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>Time since last menses (years)</td>
<td>11.8 ± 9</td>
<td>17.8 ± 10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>64.81 ± 12.75</td>
<td>64.12 ± 12.35</td>
<td>ns</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>44.06 ± 2.91</td>
<td>44.89 ± 5.020</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.43 ± 0.096</td>
<td>2.42 ± 0.10</td>
<td>ns</td>
</tr>
<tr>
<td>Phosphatemia (mmol/l)</td>
<td>1.14 ± 0.15</td>
<td>1.12 ± 0.16</td>
<td>ns</td>
</tr>
<tr>
<td>25(OH)D (nmol/l)</td>
<td>47.22 ± 27.54</td>
<td>47.48 ± 24.85</td>
<td>ns</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>34.11 ± 17.99</td>
<td>37.29 ± 22.20</td>
<td>ns</td>
</tr>
<tr>
<td>Ctx (ng/ml)</td>
<td>0.766 ± 0.367</td>
<td>0.809 ± 0.349</td>
<td>ns</td>
</tr>
<tr>
<td>bALP (ng/ml)</td>
<td>15.34 ± 6.83</td>
<td>16.61 ± 6.31</td>
<td>ns</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>22.81 ± 10.31</td>
<td>23.51 ± 9.99</td>
<td>ns</td>
</tr>
<tr>
<td>LS BMD (g/cm²)</td>
<td>0.984 ± 0.117</td>
<td>0.800 ± 0.107</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LS T-score</td>
<td>−0.473 ± 1.082</td>
<td>−2.175 ± 0.994</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neck BMD (g/cm²)</td>
<td>0.740 ± 0.096</td>
<td>0.626 ± 0.087</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neck T-score</td>
<td>−0.750 ± 0.898</td>
<td>−1.817 ± 0.810</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total hip BMD (g/cm²)</td>
<td>0.904 ± 0.124</td>
<td>0.753 ± 0.103</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total hip T-score</td>
<td>−0.173 ± 1.191</td>
<td>−1.625 ± 0.995</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; B, bisphosphonate; BMI, body mass index; PTH, parathyroid hormone; Ctx, carboxyterminal telopeptide of type I collagen; bALP, bone alcalin phosphatase; SBP, sex binding protein; LS, lumbar spine; BMD, bone mineral density; ns, not significant.
The importance of age on the bone loss induced by AIs has already been mentioned [10]; furthermore, the bone loss induced by AIs has to be compared with bone loss observed in other clinical situations. The rate of bone trabecular loss, such as vertebral bone, in the first 10 post-menopausal years ranges from less than 1% to more than 5% per year [11]. The rate of bone loss induced by glucocorticoids can reach 5% during the first months [12]. Furthermore, AI-related bone loss does not continue after AIs cessation with a recovery in lumbar spine BMD and no further loss at the hip [13]. The moderate bone loss induced by AIs can explain the low incidence of fracture in this group. Only 15 women (5.6%) without bisphosphonates had an incident fracture over the 3 years, which corresponds to the annual fracture incidence previously described in the general population [14]. Women with a new fracture had a lower lumbar spine BMD at baseline, and multiple fractures occurred only in women over 75 years. The second result of this study was the fracture risk persistence despite prescribing oral bisphosphonates, calcium, and vitamin D. In patients with osteoporosis at baseline, 12 of them had a new fracture, i.e. nearly 10% of this group. Efficacy of oral bisphosphonates in the prevention of AI-induced bone loss has already been studied [6, 7, 15] but these studies encompassed small groups of patients and were not designed to study osteoporotic fracture occurrence without systematic thoracic and lumbar spine X-rays, which is the reliable way to diagnose asymptomatic vertebral fractures and thus evaluate osteoporosis severity. In our study, patients treated for 3 years with bisphosphonate treatment maintained their bone density at the three sites but without significant gain. On the one hand, the lack of bone density gain raises the question of the efficacy or of the adherence of oral bisphosphonate in this situation. On the other hand, decreased the sCTX level by 42% after 3 years of bisphosphonates is consistent with literature data [16] and seems to indicate an overall good adherence. Age is the main risk factor for fracture in osteoporosis with a relative risk about 1.5 for each decade. In our study, patients who had incident fracture (while taking bisphosphonate) had a loss of BMD at the three sites and the sCTX level barely decreased. These results could suggest a non-optimal patient adherence or gastric absorption. Intravenous bisphosphonate could be a good means to avoid the problem of adherence, it has been shown to reduce vertebral and hip fracture risk in frail patients [19] and its efficacy in the
prevention of AI-induced bone loss is already well-documented [8, 20]. The effects of human monoclonal antibody denosumab, a subcutaneous antiresorptive treatment, have also been reported in the prevention of bone loss in patients treated by AIs and could be an alternative [9].

Our study has several limitations. First, this is not a randomized, controlled study but a prospective and longitudinal one. Second, we assessed the bone status at 3 years, which could be too short a time compared with AIs duration often prescribed for 5 years. However, we performed a bone health evaluation in real-life setting in a prospective design with an assessment of all fractures, including vertebral fractures by systematic vertebral X-rays, concomitant evaluation of BMD, and biochemical bone markers.

In conclusion, this study provides evidence that in postmenopausal non-osteoporotic women with breast cancer, 3 years of AIs treatment was not associated with major bone loss nor with a major increase in fracture risk. However, fracture occurrence in older women over 75 years and in women with intermediate BMD (T-scores comprised between −1 and −2.5) justifies a personal risk fracture assessment as mentioned by different recommendations [4]. In women with osteoporosis at the initiation of AI therapy, once-weekly oral bisphosphonate treatment successfully maintains bone mass but with a persisting fracture risk. Taking into account the problem of poor adherence to oral bisphosphonate therapy, the use of intravenous treatment should be discussed in these osteoporotic women, particularly if the hormonotherapy has to be prolonged over 3–5 years.

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