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REVIEW

Aromatase inhibitors-induced bone loss in early breast cancer

Jean-Jacques Body

CHU Brugmann, Department of Medicine, Université Libre de Bruxelles, Brussels, Belgium.

Women with breast cancer have an increased prevalence and incidence of fractures. This increased risk of fracture has become most evident following the use of aromatase inhibitors (AIs) as standard adjuvant therapy. AI-induced bone loss occurs at more than twice the rate of physiologic postmenopausal bone loss. Moreover, peripheral quantitative computed tomography data indicate that effects of AIs on bone strength and on cortical bone have been substantially underestimated by dual-energy X-ray absorptiometry. All AIs have been associated with an increased fracture risk. The incidence of fractures is at least 33–43% higher in AI-treated patients than in tamoxifen-treated patients, and this increase in fracture risk is maintained at least for the duration of AI therapy. Over the last few years, clinical trials have established the effectiveness of bisphosphonates and denosumab to preserve and even increase bone mineral density (BMD) during adjuvant AIs. Most data have been obtained with zoledronic acid administered twice a year, which effectively maintains or increases BMD in women receiving AIs. In addition, zoledronic acid has been shown to delay disease recurrence and maybe prolong survival in women with hormone-responsive tumors, thereby providing an adjuvant antitumor benefit besides preserving BMD. It is likely that a combined fracture risk assessment will more accurately identify women with breast cancer who require bone protective therapy. The FRAX tool probably underestimates the net increase in fracture risk due to AI therapy. Recent guidelines for the prevention of AI-induced bone loss have adequately considered the presence of several established clinical risk factors for fractures, in addition to BMD, when selecting patients to be treated with inhibitors of bone resorption.

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Introduction

During the last several years, the preeminence of tamoxifen for the hormonal treatment of breast cancer has been challenged by the aromatase inhibitors (AIs). The efficacy of AIs in advanced breast cancer prompted the development of multiple clinical trials evaluating their role in the adjuvant setting.[1] AIs have become the gold standard adjuvant treatment after surgery for postmenopausal women with hormone-receptor-positive breast cancer.[2,3] AIs have shown significant advantages in terms of progression-free survival and especially distant recurrences compared with tamoxifen in large randomized controlled adjuvant therapy trials, whether given up-front or sequentially.[4–7] AIs are generally administered during 5 years but more prolonged use is being investigated. Anastrozole and letrozole are non-steroidal inhibitors (type I, reversible) whereas exemestane is a steroidal (type II, irreversible) inhibitor of the aromatase enzyme, which converts androgens into estrogens. This conversion is the main source of endogenous estrogens in postmenopausal women.[8] In contrast, tamoxifen remains the hormonal treatment of choice in premenopausal women and a GnRH analog, such as goserelin, is a reasonable alternative.[9] Combined hormonal therapy with goserelin plus tamoxifen or anastrozole has been evaluated in the landmark study of the Austrian Breast and Colorectal Study Group in premenopausal women (ABCSG-12 trial). Updated results have shown that overall survival was worse with anastrozole than with tamoxifen.[10] AIs have thus no place in the adjuvant treatment of breast cancer in premenopausal women but, ironically, ABCSG-12 is the trial that has first shown remarkable benefits of zoledronic acid beyond bone loss prevention (see below).

Several other mechanisms than therapy with AIs contribute to bone loss in breast cancer patients and it appears that breast cancer itself, in the absence of bone metastases, increases the fracture rate.[11]

Is Fracture Risk Increased in Women with Breast Cancer Before Therapy with AIs?

Several reports indicate that women with breast cancer, even in the absence of skeletal metastases, have a higher rate of

Correspondence: Dr J-J Body, CHU Brugmann, Department of Medicine, Université Libre de Bruxelles, 4 Place Van Gehuchten, 1020 Brussels, Belgium.
E-mail: jean-jacques.body@chu-brugmann.be

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fractures than women of the same age without breast cancer. A case–control study performed before AIs were part of standard medical practice showed that women with breast cancer and non-metastatic disease had a higher rate of fractures compared with age- and weight-matched controls.[12] Compared with healthy controls or women evaluated at the time of breast cancer diagnosis, a five- to sixfold higher prevalence of vertebral fractures was found in women with soft tissue relapse but without evidence of bone metastases. These data are rendered even more compelling by the investigators' caveat that the risk of vertebral fractures may have been underestimated because ~50% of the study patients were taking clodronate.[12] A high incidence of vertebral fractures has been reported in a more recent study of women with breast cancer, which has been essentially attributed to the premature menopause induced by cancer chemotherapy.[13] Results from the Women's Health Initiative Observational Study indicate, however, that postmenopausal survivors of breast cancer are at increased risk for clinical fractures independently of chemotherapy-induced menopause. Five-thousand nine-hundred and twenty-eight breast cancer survivors were compared with 80 848 women who had no cancer history at baseline. After a median follow-up of 5.1 years, the hazard ratio of breast cancer survivors to women in the control group was 1.31 (95% confidence interval (CI), 1.21–1.41) for all fractures combined. This increased risk of fracture was significant regardless of age and was not limited to asymptomatic vertebral fractures. The hazard ratio (HR) fell to 1.15 (95% CI, 1.05–1.25) but remained significant after adjustment for factors related to hormone levels, fracture history, risk of fall, comorbidities and lifestyle.[14]

In the pivotal trials of AIs in the adjuvant setting, baseline bone mineral density (BMD) status was not reported and the prevalence of fractures before AI therapy has been studied only recently. BMD was measured in a prospective cohort of 343 unselected postmenopausal Spanish women recruited before adjuvant AI therapy (mean age 62 years). Only 17.7% had normal BMD values; 60.1% had osteopenia and 22.2% were osteoporotic. Prevalence of fracture (self-reported and detected using spine X-rays) was 11.4%.[15] The results of another recent prospective study go along the same line. Four hundred and ninety-seven patients aged 64±10 years were assessed before AI therapy. They had an evaluation of risk factors for fracture, blood tests, BMD measurement and systematic spine X-rays, which were assessed semiquantitatively. Thirty-one percent had a *T*-score < -2.0 at one of the three site measurements, a value that is considered by many groups as a therapeutic intervention threshold (see below). Nineteen percent had a history of non-vertebral fractures and 20% had at least one vertebral fracture detected on spine X-rays compared with a 12% age-standardized estimated prevalence in women of the same age.[16] These two studies suffer, however, from the absence of an internal control group.

Taken globally, these various studies suggest that there is an increased risk of fracture in breast cancer patients before any therapy, even if there is no explanation for this surprising finding. Indeed, surrogate markers of lifetime exposure to estrogen, such as late menarche, early menopause and a low body mass index, are associated with an increased risk of osteoporotic fractures, whereas early menarche, late menopause, postmenopausal use of HRT and high body mass index are known risk factors for breast cancer. Risk factors that increase breast cancer incidence should thus protect from osteoporotic fractures. Moreover, several studies have reported that women with higher BMD have a greater risk of breast cancer compared with women with lower BMD (reviewed in Tremollieres and Ribot[17]). The reports of an increased fracture rate in breast cancer before antineoplastic treatment are thus surprising. This increased risk could be due to the secretion by breast cancer cells *in situ* of factors, such as parathyroid hormone-related peptide or various cytokines, that induce osteoclast activation. Moreover, tumor cells are known to be able to invade the bone marrow where they could lead to local subclinical osteolysis before bone metastases are diagnosed. The presence of disseminated tumor cells in the bone marrow has been recently confirmed to have a negative prognostic influence on metastasis-free survival and breast cancer-specific survival.[18] The presence of circulating tumor cells is also clinically relevant and they provide additional prognostic information to the presence of disseminated tumor cells in the bone marrow. They have shown some clinical utility in metastatic breast cancer, where their presence inversely correlates with progression-free survival and overall survival. Moreover, it has been recently demonstrated that the presence of one or more circulating tumor cells predicts early recurrence and survival in non-metastatic breast cancer, demonstrating their pathogenic importance.[19]

AIs-Induced Bone Loss

The increased risk of bone loss and fracture in breast cancer patients has become more evident following the use of AIs as adjuvant therapy.

In premenopausal women, chemotherapy-induced premature menopause leads to a marked decrease in BMD within a short period of time.[20] In addition to chemotherapy-induced menopause, reversible ovarian suppression with goserelin has also been associated with similarly rapid rates of BMD loss (up to 7.7% within the first year).[21] The effect of goserelin-induced ovarian suppression in combination with AIs in this population is even more severe, with reports of up to 17.3% BMD loss within 3 years compared with baseline ($P < 0.0001$) in the ABCSG-12 study.[21]

In postmenopausal women with breast cancer, treatment-induced bone loss is essentially due to AI therapy. AI-induced bone loss occurs at more than twice the rate of physiologic postmenopausal bone loss.[22] Women undergo an accelerated, transient phase of bone loss during natural menopause (~3% per year during the first 1–2 years), slowing to ~1% annually thereafter.[23] AI-associated bone loss continues throughout the duration of therapy, and averages ~2% per year.[22,24] It is estimated that > 30% of patients treated with an AI will have a diagnosis of osteoporosis in the subsequent years.[25] The negative effect of estrogen depletion on bone appears to be associated with both steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs,[13,26] although the former could induce less bone loss. A comparative study analyzing the data from the same pivotal trials found significant BMD reductions in patients under anastrozole: −2.3, −4.0, −6.1% (at lumbar spine) and −1.5, −3.9, −7.2% (total hip) after 1, 2 and 5 years, respectively.[27] Treatment with letrozole resulted in comparable bone loss: −3.3, −5.3% (lumbar spine) and −1.4, −3.6% (total hip) after the first and the second year. Decrease in BMD was apparently lower in patients treated with exemestane, possibly related to its steroidal structure: −1.7, −1.0% (lumbar spine)

and −1.4, −0.8% (total hip) at 6 and 24 months, respectively.[27] These data were confirmed in a recent meta-analysis showing significant BMD reductions both at lumbar spine and total hip: −6.1 and −7.2% for anastrozole at 5 years, −5.3 and −3.6% for letrozole after 2 years, −4.0 and −2.0% for exemestane at 2 years.[28]

Importantly, effects of AIs on bone strength might have been substantially underestimated because the data summarized above relied on dual-energy X-ray absorptiometry (DXA). In a nested safety substudy from the large exemestane breast cancer prevention placebo-controlled study, 351 women were followed during 2 years by DXA and high-resolution peripheral quantitative computed tomography (distal radius and distal tibia). Included women had *T*-scores above −2.0. At the time of clinical cutoff, 242 women had completed 2-year follow-up. The decline in volumetric BMD by quantitative computed tomography was two to three times larger than the decline in areal BMD assessed by DXA. Additionally, in the exemestane group, cortical thickness and area both declined by almost 8% in the exemestane group compared with a 1% decline in the placebo group.[29] The microarchitectural deterioration associated with AIs is thus not fully reflected by changes in areal BMD on DXA. Cortical bone is also more affected than trabecular bone by exemestane and probably other AIs as well.[29] This is important because 80% of our bone mass is cortical and 80% of all fractures occur in non-vertebral sites that are mainly cortical.[30]

All AIs have also been associated with an increased fracture risk in clinical trials. In long-term follow-up of phase III trials of AIs vs tamoxifen as adjuvant therapy for early-stage breast cancer, the incidence of fractures was reported to be 33–43% higher in AI-treated patients compared with tamoxifen.[4,31,32] This increase in fracture risk is maintained at least for the duration of AI therapy. The risk appears to wane after completion of treatment[31] but more robust off-treatment data are needed to confirm this observation. Incidence of fractures in the pivotal AIs trials has been recently reviewed[33] and will only be summarized here. Anastrozole was associated with a higher risk of fracture at 5 years[34] and at 7 years compared with tamoxifen.[35] Also letrozole was associated with a long-term (up to 5 years) higher risk of fracture if compared with tamoxifen in the initial report of the Breast International Group 1–98 trial (6.5% vs 9.3%, respectively),[32] as well as in updated reports (5.7% vs 4.0%).[36] The steroidal AI exemestane was also associated with a higher risk of fractures after 1 year (7% vs 5%) and 3 years (3.1% vs 2.3%) when compared with tamoxifen.[37] Overall, the risk of fractures in patients treated with AIs seems to be higher in peripheral skeletal sites than spine or hip,[38] a possible explanation for that being represented by the younger age of patients if compared with the studies carried out for the prevention of osteoporotic fractures.[33] Importantly, fractures occurring in all the trials in patients treated with AIs were reported as adverse events of oncology trials, thus not representing primary end points of the studies, which is a likely source of underreporting and underestimation of fracture incidence. On the other hand, because the fracture rates related to the use of AIs have almost always been reported in comparison with those of tamoxifen, this could overestimate the effect of AIs because of the protective effect of tamoxifen on fracture risk, albeit this effect is controversial.[38]

Overall, because AIs are now replacing tamoxifen as the treatment of choice for postmenopausal women with early-stage breast cancer, steps should be taken to identify patients at risk for fractures to ensure proper prophylactic treatment. This class effect highlights the necessity to monitor bone loss and fracture risk in all patients receiving AI therapy, and indicates that pharmacotherapy may be needed in some patients to prevent bone loss and reduce fracture risk.

Prevention of AIs-Induced Bone Loss

Calcium and vitamin D. Before starting adjuvant AI therapy, a biochemical survey should include determination of calcium, parathyroid hormone and vitamin D levels, to exclude primary hyperparathyroidism and to diagnose vitamin D insufficiency or deficiency. Vitamin D deficiency is very common among the general population, including postmenopausal women.[39] The frequency of vitamin D insufficiency or deficiency could be even higher in breast cancer patients.[16] Secondary hyperparathyroidism resulting from chronically low serum concentrations of vitamin D attenuates the antiresorptive action of bisphosphonates, thereby leading to a higher risk of fractures if compared with patients with normal circulating levels of vitamin D.[40] In conjunction with calcium, an antifracture effect has been demonstrated for vitamin D, but clinical trials and even meta-analyses have not consistently confirmed that vitamin D supplementation in older adults prevents fractures. To reconcile these conflicting data, Bischoff-Ferrari *et al.*[41] recently pooled participant-level data from 11 randomized controlled trials of vitamin D supplementation that involved 31 022 persons 65 years of age or older. Participants in the highest quartile of daily vitamin D intake (median, 800 IU; range, 792–2000) did have significantly lower risks for both hip fracture (HR 0.70; 95% CI, 0.58–0.86, $P<0.001$) and any non-vertebral fracture (HR 0.86; 95% CI, 0.76–0.96, $P=0.007$) compared with controls. However, there are no specific data in breast cancer patients. Besides bone and muscle, other beneficial effects of vitamin D have been suggested, but they still remain controversial.[42] A case–control study on 1394 postmenopausal breast cancer patients and 1365 controls thus showed that the 25(OH) vitamin D level was significantly associated with lower breast cancer risk, particularly at levels above 20 ng/ml.[43] However, the available evidence that vitamin D supplementation reduces cancer incidence or recurrence is inconsistent and inconclusive.[42]

Pharmacological treatment. Several clinical trials have investigated intravenous bisphosphonates and other antiresorptive agents for the prevention of AI-induced bone loss in non-osteoporotic patients. These include studies of oral ibandronate,[44] risedronate,[45] denosumab,[46] and four trials of intravenous zoledronic acid: one in premenopausal (ABCSG-12)[21] and three in postmenopausal women (Zometa/Femara Adjuvant Synergy Trials; Z-FAST, ZO-FAST, E-ZO-FAST).[47–49] Results from these trials demonstrate that up-front bone-directed therapy effectively prevents bone loss and maintains or increases BMD in women receiving AIs for early breast cancer.[50]

The efficacy of zoledronic acid 4 mg intravenously every 6 months in preventing bone loss in premenopausal patients receiving goserelin plus tamoxifen or anastrozole was demonstrated in the 3-year ABCSG-12 study involving 1803 patients

with hormone-receptor-positive breast cancer. Patients who did not receive zoledronic acid at all had a dramatic decrease both in lumbar spine and total hip BMD.[21] At 60-months median follow-up (2 years after treatment completion), patients in the zoledronic acid group experienced a 4% increase in BMD in the lumbar spine and trochanter, whereas in patients who did not receive zoledronic acid, BMD still remained below baseline levels.[51]

Trials with zoledronic acid in postmenopausal women essentially evaluated the effect of concurrent administration of letrozole 2.5 mg per day and zoledronic acid at a dose of 4 mg every 6 months from the beginning of AI treatment or as delayed additional therapy (on the basis of a BMD decrease to < -2.0 or in case of osteoporotic fracture) over a 5-year period. The Z-FAST trial enrolled 602 patients and showed an overall significant difference in lumbar spine BMD change of 4.4% at 1 year, which increased up to 6.7% at 3 years in the immediate treatment group as compared with the delayed treatment group.[47] The 5-year update from Z-FAST (357 of 602 patients have completed 5 years of treatment) shows that delaying zoledronic acid results in losses in BMD at lumbar spine and total hip of −2.4% and −4.1%, respectively. However, patients who initiated immediate zoledronic acid continue to gain BMD at lumbar spine and total hip (6.2% and 2.6%, respectively; $P<0.001$ for both vs baseline).[52] The ZO-FAST trial (1066 patients enrolled) showed comparable results. Women receiving immediate zoledronic acid gained BMD (4.4% at lumbar spine and 1.9% at total hip; $P<0.0001$ for both) vs BMD losses at both sites in the delayed zoledronic acid group (−4.9% at lumbar spine and −3.5% at total hip; $P<0.0001$ vs baseline for both).[49,53] Similar BMD gains and losses were observed in E-ZO-FAST study[48] and in the NO3CC trial at 2 years follow-up.[54]

Several studies have demonstrated the efficacy of oral bisphosphonates in preventing AI-associated bone loss. However, because of the complex trial designs of some of these studies, the numbers of patients randomly assigned to AI therapy alone vs AI therapy plus bisphosphonate are often much smaller than the overall numbers of patients enrolled. Although these studies were adequately powered to detect clinically meaningful differences in BMD, only sub-populations of osteopenic patients received oral bisphosphonates and results are often inconclusive. Therefore, the evidence for oral bisphosphonates is less robust than that for intravenous bisphosphonates. Moreover, patients' compliance and persistence with oral therapies are suboptimal, whether for osteoporotic patients treated with bisphosphonates,[55] or even for patients in the adjuvant setting with potentially lifesaving interventions.[56] The oral bisphosphonate trials have been summarized elsewhere[33] and only two trials will be reviewed. The ARIBON trial included 131 postmenopausal patients treated for 2 years with anastrozole.[44] Fifty osteopenic women were randomized to receive oral ibandronate 150 mg once a month or not. Ibandronate-treated women showed positive BMD changes (+3.0 and +0.6% at lumbar spine and total hip, respectively) when compared with those not receiving ibandronate (−3.2 and −3.9% at lumbar spine and total hip, respectively).[44] The primary end point of the SABRE (Study of Anastrozole with the Bisphosphonate Risedronate) trial was to determine lumbar spine BMD changes from baseline after 2 years of treatment with anastrozole alone or in combination with risedronate (35 mg once weekly) in 154 patients.[45] After 2 years, risedronate-treated patients showed a +2.2% and +1.8% BMD increase at lumbar spine and total hip, respectively ($P<0.0001$ for each vs placebo).[45] Similar results were noted in older or smaller trials.[33]

The effects of denosumab have been explored in the HALT-BC trial (The Hormone Ablation Bone Loss Trial in Breast Cancer). This trial has randomized 252 AI-treated postmenopausal women with hormone-receptor-positive non-metastatic breast cancer to receive placebo or denosumab 60 mg subcutaneously every 6 months.[57] After 2 years, patients assigned to denosumab treatment had a higher BMD than those in the placebo group, both at lumbar spine (difference of 7.6%) and total hip (difference of 4.7%; $P<0.0001$ for both). It is important to mention that none of these trials documented an anti-fracture effect of preventive therapy with either bisphosphonates or denosumab, most probably because the studies were not designed for a fracture prevention end point and did not include a sufficient number of patients. The ongoing Austrian Breast and Colorectal Cancer Study Group Trial-18 (NCT00556374) compares denosumab with placebo in close to 3500 postmenopausal women receiving adjuvant AI therapy and should provide additional data to confirm the efficacy and determine the long-term safety of denosumab in this setting.

Additional Benefits of Prevention of AI-Induced Bone Loss

In addition to the prevention of bone loss, it has been shown that the addition of zoledronic acid to adjuvant endocrine therapy may also improve the clinical outcomes (that is, delay disease recurrence in bone and other sites) compared with endocrine therapy alone in pre- and postmenopausal women with early-stage hormone-responsive breast cancer. The efficacy of zoledronic acid in improving disease-free survival was first shown in premenopausal patients in the ABCSG-12 trial. Administration of zoledronic acid and anastrazole or tamoxifen improved disease-free survival by 32% vs anastrazole or tamoxifen alone.[51] The reduced risk of recurrence was not limited to bone sites, but was also seen at extra-skeletal sites. The benefit was maintained at 76-months' median follow-up (HR 0.73; $P=0.021$), and overall survival was significantly increased in the zoledronic acid group at this time point (HR 0.59; $P=0.042$).[58]

The Z- and ZO-FAST studies were similarly designed to evaluate zoledronic acid prevention of bone loss as a primary end point, but the authors also assessed disease recurrence and survival as secondary end points. The 3-year results showed a longer disease-free survival, with a 41% risk reduction of disease recurrence or death in patients who started concurrently letrozole and zoledronic acid (upfront arm), compared with the delayed treatment arm (HR 0.59; 95% CI, 0.36–0.96, $P=0.03$).[53] Interestingly, in both trials, local and distant recurrences were reduced by zoledronic acid treatment. In the ZO-FAST study, fewer patients receiving immediate zoledronic acid experienced bone metastases compared with patients who received delayed zoledronic acid (9 vs 17); these patients had also fewer local recurrences (2 vs 10) and fewer distant non-bone metastases (20 vs 30).[53] This disease-free survival benefit with immediate zoledronic acid was recently reported to be maintained at 60 months with a reduction of recurrences both in and outside bone (HR 0.66; $P=0.03$).[59] The anticancer effect of zoledronic

acid was also suggested in the companion trial Z-FAST, but the benefit did not reach statistical significance, probably because of the small size of the trial.[47]

The long treatment interval of zoledronic acid administration and the long-lasting effects on disease recurrence and possibly survival militate in favor of indirect rather than direct antitumor mechanisms.[60] Early administration of zoledronic acid might alter the release of factors from the bone matrix that are required for the seeding and growth of cancer cells in the bone marrow. Zoledronic acid might thus block the retention of disseminated tumor cells in the bone marrow and/or interfere with the attachment and survival of circulating tumor cells. The reduction in non-bone recurrences could be due to an inhibition of tumor self-seeding by circulating or disseminated tumor cells.[60] The initial results of the adjuvant AZURE trial are in agreement with these beneficial effects in hormone-deprived women, as positive findings were only observed in postmenopausal women. A preplanned analysis indicated that, when considering overall survival, the adjusted HR was 0.71 for the established postmenopausal women, a significant 29% improvement ($P=0.017$).[61] Zoledronic acid might thus prevent breast cancer recurrences at multiple sites when endogenous estrogen levels are low. However, the mechanisms of the antitumor effects of zoledronic acid under estrogen deprivation remain largely unknown.

Whom to Treat?

In addition to AI therapy, postmenopausal women with breast cancer may have fracture risk factors that are independent of their breast cancer therapy, but nonetheless increase their fracture risk. BMD is an established key determinant of fracture risk. Although BMD is a good surrogate for bone strength, a substantial proportion of women with fractures do not have osteoporosis at DXA.[62,63] This may be related to the fact that BMD does not capture many factors that influence bone strength, such as bone size, bone geometry and bone quality.[64] Several clinical risk factors easily captured that are independent of BMD have been shown to significantly increase fracture risk.

Currently, an overall risk assessment is recommended by the WHO[65] and the National Osteoporosis Foundation,[66] which suggest using the FRAX[67] tool to compute fracture risk. The FRAX algorithm uses the femoral neck BMD *T*-score (if available), age, body mass index, personal and family history of fractures, corticosteroid treatment, lifestyle factors (smoking and alcohol consumption), and comorbidities (rheumatoid arthritis; secondary osteoporoses) to compute the 10-year risk of hip and major osteoporotic fractures.[67,68] The FRAX tool represents an important advance in understanding and accounting for the multifactorial nature of fracture risk and has been customized for various countries and ethnicities where epidemiologic data are available. The greatest benefit of the FRAX tool is the consideration of clinical risk factors for fracture, and not only BMD, in the decision to prescribe an antiosteoporotic treatment. Recent guidelines for the prevention of AI-induced bone loss have adequately considered the presence of such risk factors for the selection of patients to be treated with inhibitors of bone resorption.

Estimation of fracture risk in women with breast cancer has, however, a further level of complexity in that the disease and its treatment can, by themselves, alter BMD and fracture risk. As the FRAX tool has been validated using population-based studies in generally healthy postmenopausal women, it might not take into sufficient account the factors specific to breast cancer, such as the effect of anticancer therapies that induce bone loss and alter bone quality.[29,33,69] Furthermore, FRAX does not adjust for a 'dose–response' in fracture risk factors; this might be especially relevant in the breast cancer setting, wherein long-term treatment with AIs would be included under the single 'secondary osteoporosis' feature in the FRAX tool, thereby resulting in a marked underestimation of the net increase in fracture risk. Although some guidelines (for example, American Society of Clinical Oncology (ASCO) guidelines) continue to recommend thresholds for bone-directed therapy based primarily on BMD, recent clinical guidelines for patients starting AIs have included fracture risk factors for patient assessment and treatment decisions. Such algorithms for fracture risk assessment specifically in the breast cancer setting should help guide treatment decisions to preserve bone health in such patients.

An international expert panel recommended the treatment of all patients with *T*-score $\leqslant -2.0$, but also those subjects presenting at least two of the following risk factors: *T*-score < -1.5; age >65 years; body mass index $<20\,kg\,m^{-2}$; family history of hip fracture; personal history of fragility fracture after 50 years of age; oral corticosteroid therapy >6 months; cigarette smoking. The panel suggested that the BMD of patients treated with oral bisphosphonates or not receiving any antiosteoporotic drug be monitored every 1–2 years. On the other hand, postmenopausal women treated with AIs should undergo a regular clinical assessment of their risk status.[50,62] Therefore, as long as antiresorptive therapy to prevent additional bone loss is initiated, osteoporosis (with or without a history of fractures) is not a contraindication for AI therapy in postmenopausal women with early breast cancer. The panel recommended that antiresorptive therapy be continued as long as AI therapy is maintained, currently most often 5 years.[50] The preference was given to zoledronic acid 4 mg every 6 months as it is the only antiresorptive agent with demonstrated efficacy and safety over such a long duration.[50,62] The most comprehensive fracture risk assessment algorithm for patients with early breast cancer is described in a position statement from an expert panel in the United Kingdom.[69] This algorithm classifies patients into low-, intermediate- and high-risk groups for fracture based on hormonal status (for example, premature menopause and use of AIs), fracture history, secondary osteoporosis and BMD changes during adjuvant therapy for breast cancer.[69] The authors considered all bisphosphonates as appropriate. Although quite complete, this algorithm is probably too complex to be largely used.

A European Society for Clinical and Economical aspects of Osteoporosis and Osteoarthritis working group recommends that all women starting therapy with AIs should be carefully assessed for their baseline risk of osteoporotic fractures by performing a DXA examination and a full evaluation of all the clinical risk factors (including age, parental fracture history, body mass index $<20\,kg\,m^{-2}$, corticosteroids use, cigarette smoking, nutritional intakes, disuse, tendency to falls and conditions associated to osteoporosis). The working group recommends that antiresorptive treatment should be started in all osteoporotic women, and—irrespective of BMD—in all women older than 75 years and in all patients with a prevalent fragility fracture. Although the authors acknowledge that the evidence is less strong, they recommend that postmenopausal women with *T*-score below -1.5 presenting at least one

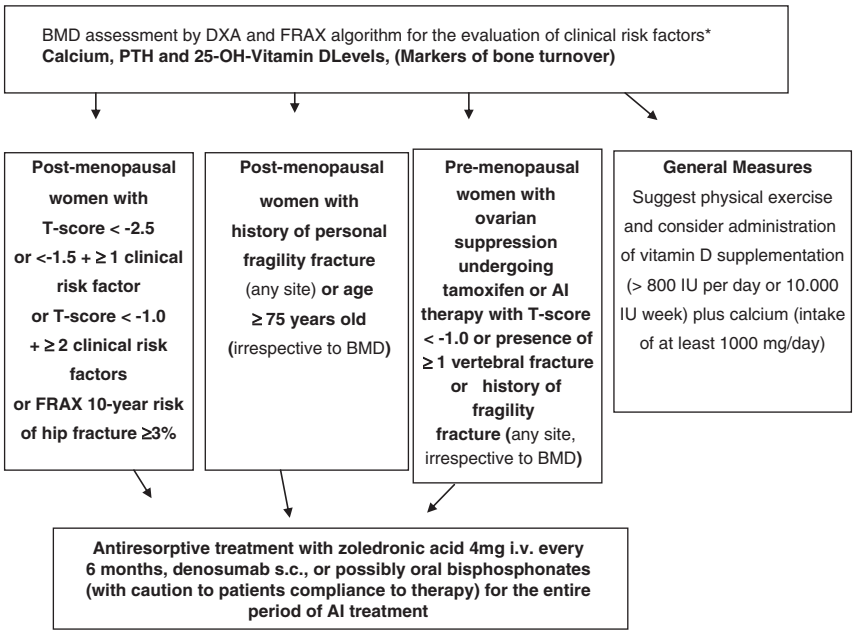

Figure 1 Approach to patients with breast cancer treated with AIs (from Rizzoli R *et al*[33]).

clinical risk factor should be treated, as well as those with a *T*-score between −1.0 and −1.5 and presenting at least two clinical risk factors (**Figure 1**). Alternatively, therapy could be considered in patients with a FRAX-determined 10-year hip fracture probability ⩾3%, which corresponds to the intervention threshold suggested in many countries (or a probability for major osteoporotic fractures of 20%).[33]

Despite the growing recognition of the frequency and the consequences of AI-induced bone loss, there are currently no therapies specifically approved for its prevention. The most robust data currently available in terms of the numbers of patients treated and the duration of follow-up support the use of zoledronic acid (4 mg twice a year) to prevent AI-induced bone loss.[47–49] Smaller trials also support the activity of oral bisphosphonates. However, a critical issue is patients' adherence to oral antifracture therapy and a switch to intravenous therapy is generally recommended if non-adherence to oral drugs is suspected. In addition, the delay in disease recurrence observed in the trials of zoledronic acid supports the potential for anticancer benefits from a therapy designed to preserve bone integrity.[51–53] Such an effect, in terms of recurrence reduction, has not been reported so far in breast cancer for other antiresorptives, notably denosumab, which represents a new treatment option more effective than zoledronic acid in patients with bone metastases.[70] Ongoing trials are evaluating whether other bisphosphonates and denosumab might also provide similar benefits,[71] and the results are eagerly awaited.

The rationale behind these experts consensus to select patients for the prevention of AI-induced bone loss is evident and makes common sense. However, one might wonder if such careful patient selection is really mandatory. One might indeed consider that there are good reasons to administer potent inhibitors of bone resorption in all patients starting AI therapy in the adjuvant setting. Bone resorption-induced release of growth factors from the bone matrix stimulates breast cancer cells growth and their secretion of osteolytic factors;[72] all AIs increase bone resorption and fracture rate apparently independently of baseline BMD and clinical risk factors for fracture; and prevention of AI-induced bone loss is safe and, at least for zoledronic acid, provides important and clinically relevant anticancer benefits. The cost-effectiveness and safety of such an unselected approach should, however, be studied in adequately designed prospective trials.

Conclusions

Several studies indicate that women with breast cancer before antitumor treatment have an increased fracture risk compared with age-matched women without breast cancer. In addition to established risk factors such as BMD, women with breast cancer may be exposed to numerous factors that reduce bone strength and structural integrity. The most notable fracture risk factors include advancing age (>65 years), AI therapy, chemotherapy-induced menopause, low body-mass index ($<20\,kg\,m^{-2}$), a family history of hip fracture, a personal history of fragility fracture, corticosteroid use, excessive alcohol consumption and smoking.[72,44] Although specific data for cancer patients are not available, the combination of these genetic, environmental and cancer treatment-related factors is likely to contribute to the increased fracture risk observed in women with breast cancer, especially women receiving AI therapy.

Although none of the trials designed to prevent AI-induced bone loss specifically addressed the influence of clinical risk factors on fracture risk in this patient population, it is logical to infer that bone-directed therapy will be essential in women receiving AIs who also have multiple fracture risk factors. It is likely that

a combined fracture risk assessment rather than BMD alone will more accurately identify women with breast cancer who require bone protective therapy. Oral and intravenous bisphosphonates and denosumab have all been shown to prevent AI-induced bone loss. In addition, emerging anticancer benefits (for example, reduced disease recurrence, improved disease-free survival and prolonged overall survival) from intravenous bisphosphonates provide additional reasons to proactively use these agents during adjuvant AI treatment.

Conflict of Interest

J-JB is a consultant for and has received lecture fees from Amgen and Novartis.

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