Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment

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Received 28 October 2010; revised 7 January 2011; accepted 10 January 2011

Background: Bone mineral density (BMD)-based guidelines for bone-directed therapy in women with early breast cancer (EBC) appear inadequate for averting fractures, particularly during aromatase inhibitor (AI) therapy. Therefore, an algorithm was developed to better assess risk and direct treatment (Hadji P, Body JJ, Aapro MS et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol 2008; 19: 1407–1416). Here, we provide updated guidance on pharmacologic interventions to prevent/treat aromatase inhibitor-associated bone loss (AIBL).

Design: Systematic literature review identified recent advances in preventing/treating AIBL. Individual agents were assessed based on trial size, design, follow-up, and safety.

Results: Fracture risk factors in patients with EBC remain unchanged (Hadji P, Body JJ, Aapro MS et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol 2008; 19: 1407–1416). The World Health Organization Fracture Risk Assessment Tool algorithm includes fracture risk factors plus BMD but does not adequately address AIBL effects. Several antiresorptives can prevent/treat AIBL. However, concerns regarding compliance and long-term efficacy/safety remain. Overall, evidence is strongest for twice-yearly zoledronic acid (ZOL), and recent advances support additional anticancer benefits from ZOL.

Conclusions: All patients initiating AIs need advice regarding exercise, calcium/vitamin D supplements, baseline BMD monitoring (when available), and bone-directed therapy if T-score <−2.0 or at least two fracture risk factors were observed. Patients with T-score > −2.0 and no risk factors should be managed based on BMD loss during years 1–2. Unsatisfactory compliance/decreasing BMD after 12–24 months on oral bisphosphonates should trigger a switch to i.v. bisphosphonate.

Key words: aromatase inhibitor, bisphosphonate, bone loss, breast cancer, fracture risk, zoledronic acid

Introduction

Skeletal homeostasis is achieved through coupled and balanced bone resorption and bone formation. Several local and systemic factors regulate these processes, including estrogen, a key negative regulator of osteolysis. As a consequence, physiologic decreases in estrogen levels place postmenopausal women at high risk for osteoporosis [low bone mineral density (BMD)] and fractures, and this risk can be exacerbated by breast cancer and its therapies [1]. Systemic therapies for breast cancer can indirectly interfere with skeletal homeostasis, either through their effects on gonadal steroid hormone production or by inhibiting peripheral aromatization into estrogen [1]. In addition, some therapies for breast cancer might directly affect bone formation [2]. Regardless of the underlying mechanism, patients with breast cancer and other malignancies are at risk for cancer treatment-induced bone loss. The majority of breast malignancies are hormone responsive, and adjuvant endocrine therapy is used extensively to treat such disease [3, 4].

Tamoxifen was the past treatment of choice for endocrine-responsive breast cancer and was found to preserve BMD in postmenopausal (but not premenopausal) women [5], although fracture risks remained similar in postmenopausal women regardless of whether they were receiving tamoxifen [6]. However,
aromatase inhibitors (AIs) now have largely replaced tamoxifen as the treatment of choice for hormone-responsive breast cancer in postmenopausal women because of better relapse-free survival, although no significant overall survival benefits have been reported [3, 4]. Because AIs prevent peripheral estrogen production, they suppress estrogen levels beyond what is achieved by natural menopause, thereby leading to accelerated bone loss [7]. Indeed, aromatase inhibitor-associated bone loss (AIBL) occurs at more than twice the rate of physiologic postmenopausal BMD loss [7]. As a result, women receiving adjuvant AI therapy for breast cancer are at increased risk for fractures [8–10], which has been shown to result in increased morbidity and mortality in women with postmenopausal osteoporosis [11, 12]. Currently, it is not clear whether the increased fracture rate seen during AI therapy will translate into increased mortality similar to that seen in women with postmenopausal osteoporosis-related fractures. Although a recent meta-analysis found no increase in mortality with AI therapy, cause-specific mortality analyses have not been conducted [13].

Recent years have seen an expanded understanding of fracture risk factors other than BMD [2], resulting in several national and international bone health guidelines being updated to provide more comprehensive insights into fracture risk assessment and clinical decision making regarding antiresorptive therapy (Table 1). A retrospective case-controlled study in 402 postmenopausal women with newly diagnosed breast cancer demonstrated that a combination of BMD and clinical risk factors identified >28% of these women as candidates for bone-directed therapy, compared with <10% identified by BMD criteria alone [19]. A key advance in this field has been the development of the World Health Organization Fracture Risk Assessment Tool (FRAX®) algorithm (http://www.sheffield.ac.uk/FRAX/). This is an easy-to-use online tool for assessing fracture risk in postmenopausal women with or without BMD data, adapted for different countries [20]. The FRAX algorithm is based on data from large-scale population-based cohorts from different parts of the world and uses factors such as age, body mass index (BMI), smoking history, personal and family histories of fracture, glucocorticoid use, and secondary causes of osteoporosis to assess long-term fracture risk. However, FRAX is not designed to assess fracture risk in women with breast cancer and indeed may substantially underestimate the effect of AI therapy—the ‘secondary osteoporosis’ option in the FRAX tool has a much smaller effect on fracture risk than would be expected for AI therapy. Moreover, as clinical trials comparing AIs with tamoxifen mature, it is evident that AIs have a large effect on acute fracture risk during active treatment [9, 10], which might be underestimated by FRAX, an algorithm designed to provide long-term (10-year) fracture risk (P. Hadji, unpublished data). During the off-treatment follow-up period in clinical trials of AIs, fracture rates have been observed to decrease to baseline, suggesting that AI treatment might not substantially affect long-term fracture risk (i.e. as estimated by FRAX) in breast cancer survivors [9]; however, such follow-up is limited to a small proportion of enrolled patients, and information regarding bisphosphonate use (an important variable in influencing fracture risk) is not available in these datasets. None the less, the increase in fracture risk during the course of AI treatment poses a real and clinically relevant challenge to patients’ overall well-being. Finally, the increase in bone turnover during AI treatment might alter the bone microarchitecture in addition to reducing BMD. To date, the possible interactions between AI-related alterations in bone structure and fracture risk are poorly understood, and it is not known whether the bone microarchitecture can fully recover after stopping AI therapy.

The last 2 years have also seen the maturation of several clinical trials evaluating the use of antiresorptive agents, such as bisphosphonates and denosumab (an mAb against the receptor activator of nuclear factor kappab ligand), for preventing and/or treating AIBL. In addition, data supporting an anticancer role for bisphosphonates [especially zoledronic acid (ZOL)] are rapidly accumulating. Furthermore, population-based case-control studies suggest that oral bisphosphonate treatment of postmenopausal osteoporosis may reduce the incidence of invasive breast cancers [21–23]. Early trials of adjuvant clodronate for preventing bone metastases in early breast cancer (EBC) were promising but inconclusive [24–27]. Recently, two phase III trials have demonstrated improved disease-free survival when adjuvant ZOL [4 mg every 6 months (q6mo)] is combined with endocrine therapy for EBC [28, 29] and better progression-free and overall survival with combinations of monthly ZOL plus standard cytotoxic therapies for multiple myeloma [30]. Moreover, phase II studies suggest direct anticancer effects of ZOL (4 mg every 3–4 weeks) on disseminated tumor cells in the bone marrow of patients with breast cancer [31–34]. A subset analysis from an ongoing trial shows that adding ZOL (4 mg every 3–4 weeks) to neoadjuvant chemotherapy can reduce residual tumor size and improve pathologic response rates compared with chemotherapy alone [35]. In light of these developments, we have updated our recommendations for preventing and treating AIBL in postmenopausal women with EBC [2].

methods

systematic literature review

A systematic review of published literature to identify factors that contribute to fracture risk in women with breast cancer was reported previously [2]. PubMed searches of Medline (National Library of Medicine, Bethesda, MD) and other databases were carried out to identify clinical trials of antiresorptive agents used for preventing and treating AIBL from June 2008 through June 2010. Additional information was obtained from abstracts presented at international meetings including the St Gallen Breast Cancer Conference, European Breast Cancer Conference, San Antonio Breast Cancer Symposium, and American Society of Clinical Oncology annual meetings and breast cancer symposia.

An evidence-based medicine approach was used to determine when to initiate antiresorptive therapy for AIBL, to determine the appropriate antiresorptive therapy, and to define follow-up/monitoring procedures. All authors reviewed the available evidence and as a group reached a consensus regarding the levels of evidence and treatment recommendations.

Identifying fracture risk in women with breast cancer

Fracture risk factors that have been validated in large prospective population-based studies in postmenopausal women were previously characterized according to their impact
Table 1. Summary of guidelines for BP use in women with breast cancer\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Source</th>
<th>Considered for treatment</th>
<th>BP</th>
<th>Dosing</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCO [14]</td>
<td>Women with T-score $\leq$ −2.5; women with T-score between −1.0 and −2.5 should receive individualized therapy</td>
<td>Alendronate</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>St Gallen [3]</td>
<td>No treatment of women with normal BMD</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>UK Expert Group [15]</td>
<td>Premenopausal women with ovarian suppression/failure and one or more of the following: AI therapy and T-score $&lt; -1.0$; T-score $&lt; -2.0$; vertebral fracture; annual bone loss $&gt;4%$ at LS or TH</td>
<td>Alendronate</td>
<td>70 mg/week</td>
<td>Follow-up at 2 years to reassess</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risedronate</td>
<td>35 mg/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ibandronate</td>
<td>150 mg p.o./month or 3 mg i.v. q3mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zoledronic acid</td>
<td>4 mg i.v. q6mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postmenopausal women receiving AI therapy with one or more of the following: T-score $&lt; -2.0$; vertebral fracture; annual bone loss $&gt;4%$ at LS or TH</td>
<td>Alendronate</td>
<td>70 mg/week</td>
<td>Follow-up at 2 years to reassess</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risedronate</td>
<td>35 mg/week</td>
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<td></td>
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<td>Ibandronate</td>
<td>150 mg p.o./month or 3 mg i.v. q3mo</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Zoledronic acid</td>
<td>4 mg i.v. q6mo</td>
<td></td>
</tr>
<tr>
<td>Belgian Bone Club [16]</td>
<td>Women with T-score $&lt; -2.5$ or history of fragility fracture; women with T-score between −1.0 and −2.5 plus other risk factors</td>
<td>Zoledronic acid</td>
<td>4 mg i.v. q6mo</td>
<td>As long as AI therapy</td>
</tr>
<tr>
<td>International Expert Panel (Hadjii et al.) [2]</td>
<td>All women receiving AI therapy with T-score $&lt; -2.0$ or any two of the following risk factors: T-score $&lt; -1.5$; age $&gt; 65$ years; low BMI ($&lt;20$ kg/m$^2$); family history of hip fracture; personal history of fragility fracture after age 50; oral corticosteroid use $&gt;6$ months; smoking</td>
<td>Zoledronic acid</td>
<td>4 mg i.v. q6mo</td>
<td>At least 2 years, possibly as long as AI therapy</td>
</tr>
<tr>
<td>International Expert Panel (Aapro et al.) [17]</td>
<td>Women with T-score $&lt; -2.0$ or T-score $&lt; -1.5$ and one or more of the following risk factors\textsuperscript{c}: AI use; age $&gt; 65$ years; corticosteroid use $&gt;6$ months; family history of hip fracture; personal history of fragility fracture after age 50</td>
<td>Zoledronic acid</td>
<td>4 mg i.v. q6mo</td>
<td>Not given</td>
</tr>
<tr>
<td>Swiss Guidelines [18]</td>
<td>All women with two or more of the following risk factors: AI therapy; T-score $\leq -1.5$; age $&gt; 65$ years; corticosteroid use $&gt;6$ months; family history of hip fracture; personal history of fragility fracture after age 50 or all women with T-score $\leq -2.0$ or T-score $\leq -1.5$ plus one other risk factor or alternatively use FRAX to determine risk</td>
<td>Any nitrogen-containing BP (most data available for zoledronic acid)</td>
<td>–</td>
<td>Not given</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Limited evidence for the use of other agents was available when these guidelines were written.

\textsuperscript{b}Calcium and vitamin D supplements are to be used in conjunction with BPs, and exercise when appropriate is recommended by most panels.

\textsuperscript{c}Two or more risk factors when T-score is unavailable.

AI, aromatase inhibitor; ASCO, American Society of Clinical Oncology; BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; GnRH, gonadotropin-releasing hormone; LS, lumbar spine; p.o., oral; q3mo, every 3 months; q6mo, every 6 months; TH, total hip.
on overall fracture risk [2]. Risk factors found to increase fracture risk in women with breast cancer included AI therapy, T-score < -1.3, age > 65 years, low BMI (<20 kg/m²), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, and smoking. These risk factors (with the exception of AI therapy) have been validated in large population-based studies in healthy postmenopausal women but not specifically in women with a history of breast cancer [2, 36, 37]. Available data suggest that BMD measurement should not be the sole criterion for determining fracture risk and that an overall fracture risk assessment that combines risk factors provides the most accurate evaluation [38]. It is also important to note that the use of corticosteroids for >6 months is an established risk factor based on data from nonmalignant disease settings. When combined with chemotherapy regimens, the doses of oral corticosteroids are typically higher and might negatively impact bone health in a shorter time. Indeed, the effect of chemotherapy plus corticosteroids on BMD is poorly understood and may differ from the effects of corticosteroids used for an inflammatory condition. Finally, to identify and manage secondary causes of osteoporosis, complete baseline laboratory assessments should include serum levels of calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone, hemoglobin, C-reactive protein, alkaline phosphatase, thyroid-stimulating hormone, and potentially also gamma-glutamyl transferase; creatinine clearance; and protein electrophoresis (serum and/or urine).

### Selecting a Treatment to Prevent AIBL

Available data from randomized clinical trials in >4100 patients suggest that i.v. and oral bisphosphonates and denosumab can effectively prevent AIBL in patients with breast cancer (Table 2). Although these trials were not designed for a fracture-prevention end point (which would require very large trial populations in this setting), data from the osteoporosis setting have demonstrated a strong correlation between BMD improvements and fracture prevention [50]. Therefore, data from the larger studies in this group may be considered as evidence for preserving skeletal health during AI therapy. However, fracture reduction is a worthwhile target in clinical trials of antiresorptive therapies for prevention of AIBL, and absolute fracture rates (in different patient subpopulations) are valuable for evaluating the cost-effectiveness of prevention measures.

#### I.v. Bisphosphonates (Level of Evidence: I)

The largest quantity of data supporting i.v. bisphosphonate therapy to prevent AIBL in postmenopausal women with EBC continues to come from four independent studies encompassing >2700 postmenopausal women with EBC [28,39–41] (Table 2). The three companion Zometa–Femara Adjuvant Synergy Trials (Z-FAST, N = 602; ZO-FAST, N = 1065; E-ZO-FAST, N = 527) compared the efficacy of ZOL (4 mg i.v. q6mo) administered in conjunction with AI therapy (immediate group) or after a BMD decrease to < -2.0 or a nontraumatic fracture (delayed group) [28, 39, 40]. The recent 61-month update from Z-FAST (357 of 602 patients have completed 5 years of treatment) showed that delaying ZOL resulted in losses in BMD at lumbar spine (LS) and total hip (TH; −2.42% and −4.12%, respectively; P ≤ 0.0003 for both versus baseline) [39]. However, patients who initiated immediate ZOL continued to gain BMD at LS and TH (6.19% and 2.57%, respectively; P ≤ 0.0003 for both versus baseline) [39]. Similar results for the 36-month analyses of the ZO-FAST and E-ZO-FAST studies confirmed that immediate ZOL not only prevents bone loss but also makes women continue to gain BMD during the 3 years of therapy [28, 40] (Table 2). In ZO-FAST, women receiving immediate ZOL gained BMD at LS and TH (4.39% and 1.9%, respectively; P < 0.0001 versus

### Table 2. Trials of Antiresorptive Agents for Preventing AIBL in Postmenopausal Women with Breast Cancer

<table>
<thead>
<tr>
<th>Antiresorptive agent (trial)</th>
<th>N</th>
<th>BMD study, n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosing</th>
<th>Treatment duration, years</th>
<th>Follow-up, months</th>
<th>Mean BMD change from baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid (ZO-FAST) [28]</td>
<td>1065</td>
<td>1065</td>
<td>4 mg i.v. q6mo</td>
<td>5</td>
<td>36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+4.39</td>
</tr>
<tr>
<td>Zoledronic acid (Z-FAST) [39]</td>
<td>602</td>
<td>602</td>
<td>4 mg i.v. q6mo</td>
<td>5</td>
<td>61</td>
<td>+6.19</td>
</tr>
<tr>
<td>Zoledronic acid (E-ZO-FAST) [40]</td>
<td>527</td>
<td>527</td>
<td>4 mg i.v. q6mo</td>
<td>5</td>
<td>36</td>
<td>+5.98</td>
</tr>
<tr>
<td>Zoledronic acid (N03(CC)) [41]</td>
<td>558</td>
<td>395</td>
<td>4 mg i.v. q6mo</td>
<td>5</td>
<td>24</td>
<td>+4.94</td>
</tr>
<tr>
<td>Denosumab (HALT-BC) [42]</td>
<td>252</td>
<td>252</td>
<td>60 mg s.c. q6mo</td>
<td>2</td>
<td>24</td>
<td>+6.2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risedronate (SABRE) [43]</td>
<td>154</td>
<td>111</td>
<td>35 mg p.o./week</td>
<td>2</td>
<td>24</td>
<td>+2.2</td>
</tr>
<tr>
<td>Risedronate [44]</td>
<td>87</td>
<td>87</td>
<td>35 mg p.o./week</td>
<td>2</td>
<td>24</td>
<td>+0.4</td>
</tr>
<tr>
<td>Clodronate [45]</td>
<td>61</td>
<td>61</td>
<td>1600 mg p.o./day</td>
<td>3</td>
<td>60</td>
<td>−1.0</td>
</tr>
<tr>
<td>Risedronate (ARBI) [46]</td>
<td>213</td>
<td>70</td>
<td>35 mg p.o./week</td>
<td>2</td>
<td>24</td>
<td>+5.7</td>
</tr>
<tr>
<td>Risedronate (IBIS-II) [47]</td>
<td>613</td>
<td>59</td>
<td>35 mg p.o./week</td>
<td>5</td>
<td>12</td>
<td>+0.32</td>
</tr>
<tr>
<td>Ibandronate (ARIBON) [48]</td>
<td>131</td>
<td>50</td>
<td>150 mg p.o./month</td>
<td>2</td>
<td>24</td>
<td>+2.98</td>
</tr>
<tr>
<td>Risedronate [49]</td>
<td>118</td>
<td>11</td>
<td>35 mg p.o./week</td>
<td>1</td>
<td>12</td>
<td>+4.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Number of patients randomly assigned to compare bisphosphonate versus placebo for BMD study.

<sup>b</sup>BMD data available for 36 months follow-up; disease recurrence outcomes available for 48 months follow-up.

<sup>c</sup>Estimates based on published graph.

AIBL, aromatase inhibitor-associated bone loss; ARBI, Arimidex Bone Mass Index and Oral Bisphosphonates; ARIBON, Arimidex-Bondronat; BMD, bone mineral density; HALT-BC, Hormone Ablation Bone Loss Trial in Breast Cancer; IBIS, International Breast Cancer Intervention Study; LS, lumbar spine; NR, not reported; p.o., oral; q6mo, every 6 months; SABRE, Study of Anastrozole with the Bisphosphonate Risedronate; TH, total hip.
delayed group for both) versus BMD losses at both sites in the delayed-ZOL group (~4.9% and ~3.5%, respectively; \( P < 0.0001 \) versus baseline for both) [28, 51]. Similar BMD gains and losses were also observed in E-ZO-FAST at 36 months follow-up [40].

Another trial examined the efficacy of ZOL (4 mg i.v. q6mo) for preventing AIBL in postmenopausal women with endocrine-responsive breast cancer who started adjuvant letrozole after completing up to 6 years of tamoxifen treatment [41] (Table 2). Similar to BMD increases seen in Z-FAST, ZO-FAST, and E-ZO-FAST, women in the N03CC trial who received immediate ZOL had significantly increased mean BMD at LS (3.66% at 12 months and 4.94% at 24 months) and TH (1.02% at 12 months and 1.22% at 24 months) compared with baseline (\( P < 0.001 \) for all comparisons) [41]. At the 12- and 24-month post-baseline assessments, women in the delayed-ZOL group lost BMD at the LS (~1.66% and ~2.28%, respectively) and TH (~1.41% and ~3.34%, respectively). Taken together, evidence from these four randomized controlled trials demonstrates that administering ZOL (4 mg q6mo) at initiation of AI therapy can effectively prevent AIBL in postmenopausal women.

ZOL (4 mg q6mo) appears to be well tolerated in postmenopausal women receiving adjuvant AI therapy for breast cancer, and the most common adverse events are transient infusion-site reactions and mild influenza-like symptoms [28, 39–41]. At median follow-up ranging from 24 to 61 months in the intent-to-treat populations of the four trials, with 1629 patients having received ZOL (upfront and delayed groups), 5 cases (0.3%) of confirmed or possible osteonecrosis of the jaw (ONJ) have been referred to the ONJ Adjudication Committees, and only 3 patients (0.18%) had grade 3/4 renal adverse events that were suspected to be related to bisphosphonate treatment [28, 39–41]. It is possible that the incidence of ONJ may be underestimated in these trials because awareness of ONJ improved after patients had already begun treatment. However, ONJ prevention and management techniques have also developed during this time period. None of the less, maintenance of good oral hygiene, preventive dental care, and regular (annual) dental assessments are advisable in women receiving bisphosphonates (i.v. or oral) for AIBL. Long-term follow-up of these patients may provide a better understanding of ONJ incidence, the role of cumulative doses of ZOL on ONJ risk, and whether ONJ risk may continue following treatment discontinuation in this patient population.

oral bisphosphonates (level of evidence: II–III)

Several randomized clinical trials have investigated the efficacy of oral bisphosphonates for preventing AIBL [43–49] (Table 2). Because of the complex trial designs of some of these studies, the numbers of patients randomly assigned to AI therapy alone versus AI therapy plus bisphosphonate are often much smaller than the overall numbers of patients enrolled. Therefore, the evidence for oral bisphosphonates is less robust than that for i.v. ZOL. The Study of Anastrozole with the Bisphosphonate Risedronate (SABRE) compared the efficacy of risedronate (35 mg/week orally) versus placebo for 2 years in postmenopausal women with hormone receptor-positive EBC receiving adjuvant anastrozole who also had a moderate risk of fragility fracture \( (n = 154) \) [43]. At 24 months, oral risedronate significantly increased LS BMD by 2.2% and TH BMD by 1.8% versus baseline (\( P < 0.0001 \) for each versus placebo). A similar trial in postmenopausal women with breast cancer receiving AI therapy demonstrated that oral risedronate (35 mg/week) initially improved BMD versus baseline but only modestly increased LS BMD (0.4%) and TH BMD (0.9%) at 24 months [44]. Among patients enrolled in the International Breast Cancer Intervention Study (IBIS-II) bone sub-study \( (n = 613) \), women with osteopenia \( (n = 59) \) receiving anastrozole plus risedronate (35 mg/week) had increased LS (0.32%) and TH (0.67%) BMD compared with women receiving anastrozole alone [47]. In the 24-month analysis of the Arimidex–Bondronat (ARIBON) study, monthly oral ibandronate (150 mg) prevented bone loss in osteopenic women \( (n = 25) \) compared with placebo \( (n = 25) \) and in a small number of patients with preexisting osteoporosis \( (n = 13) \) [48]. Oral ibandronate increased LS BMD by 2.98% and TH BMD by 0.60%. In all the studies of oral bisphosphonates, patients who did not receive a bisphosphonate experienced substantial BMD loss during AI therapy. However, although these studies were adequately powered to detect clinically meaningful differences in BMD, only small subpopulations of osteopenic patients received oral bisphosphonates in these trials. At present, long-term safety and efficacy data for oral bisphosphonates are available in the osteoporosis setting. Confirmation of these profiles in patients with EBC is necessary before stronger evidence-based recommendations can be provided for oral bisphosphonate use in the AIBL setting.

Oral bisphosphonates were generally well tolerated in these trials. However, the rigid dosing requirements for oral bisphosphonates (e.g. fasting before and after dosing, the need to remain upright after dosing) may be associated with some inconvenience for patients. Moreover, patients’ compliance and persistence with oral therapies are suboptimal [52, 53], even with potentially lifesaving interventions such as adjuvant endocrine therapy. In the case of supportive treatments such as antiresorptives, insights from the osteoporosis setting show low levels of long-term compliance. Indeed, reports of clinically relevant compliance levels over 1 year range from 20% for patients receiving daily bisphosphonates to 57% for patients receiving weekly or monthly bisphosphonates (more recent treatment paradigms) [54–56]. A study from the UK showed that the median time to discontinuing oral bisphosphate therapy is ~3 months for patients receiving daily bisphosphonates versus ~11 months for weekly, and >18 months for monthly dosing [57]. Noncompliance with oral bisphosphonates in the osteoporosis setting has been associated with increased fracture rates (i.e. poor clinical outcomes) [56, 58, 59]. Trends toward better compliance with less frequent therapy have been reported in multiple studies in osteoporotic women [60–62]. Because of the strong association between compliance and clinical outcome [61], strategies to improve patients’ compliance and persistence with oral bisphosphate therapy are necessary to ensure benefit from these agents in the AIBL setting. Moreover, recent evidence from a study in women with premature menopause attributable to treatment of breast cancer [63] suggests that oral bisphosphonates might be
insufficient to prevent AIBL in recently menopausal women or in women undergoing concomitant ovarian suppression.

denosumab (level of evidence: II–III)
The Hormone Ablation Bone Loss Trial in Breast Cancer (HALT-BC; N = 252) examined the efficacy of twice-yearly denosumab (60 mg s.c. q6mo) versus placebo for preventing AIBL in postmenopausal women with EBC receiving AI therapy [42] (Table 2). At 24 months follow-up, there was a significant 7.6% difference in LS BMD between the denosumab and placebo groups (P < 0.0001). Although the BMD change was not precisely defined, this between-group difference equates with an ~6.2% BMD increase with denosumab, versus an ~1.4% BMD loss with placebo. Similarly, there was a significant 4.7% difference in TH BMD between denosumab and placebo at 24 months (P < 0.0001), resulting from an ~3.7% increase with denosumab and a 1% loss with placebo. Although the results of this trial are promising, the use of a variety of AIs and the variable durations of prior AI therapies at baseline may have influenced outcomes. The ongoing Austrian Breast and Colorectal Cancer Study Group Trial-18 (NCT00556374) will compare denosumab with placebo in ~3460 postmenopausal women receiving adjuvant AI therapy [64] and should provide additional data to confirm the efficacy and determine the long-term safety of this novel antiresorptive agent. For example, although no ONJ was reported in the small-scale HALT-BC trial, emerging data from ongoing trials of denosumab (120 mg s.c. monthly) in the metastatic setting have revealed an ONJ risk that is at least similar to the ONJ risk during i.v. bisphosphonate (ZOL 4 mg monthly) therapy [65–67]. Therefore, preventive dental care to minimize ONJ risk is also recommended for patients initiating denosumab (60 mg s.c. q6mo) treatment, and further long-term safety data are needed to fully elucidate ONJ risks with denosumab.

treatment and follow-up recommendations for patients receiving AIs (level of evidence: I, grade of recommendation: A)

Our guidance for antiresorptive therapy to treat or prevent AIBL in women with EBC is derived from well-designed randomized controlled studies and is based on validated risk factors with or without BMD measurements (Figure 1) [2]. All patients beginning AI therapy should be advised to exercise moderately (resistance and weight-bearing exercise) and should receive calcium and vitamin D supplements. The International Osteoporosis Foundation recommends a daily intake of 1300 mg calcium and 600 IU vitamin D for postmenopausal women (guidelines available at www.iofbonehealth.org) [68]. Elderly women, or those with reduced physical activity and sunlight exposure, may need higher levels of these nutrients. Of the recommended daily calcium intake, up to 1000 mg may be in the form of a supplement. For postmenopausal women receiving AI therapy, we recommend at least 800 (and up to 2000) IU vitamin D every day.

For patients initiating AI therapy with a T-score ≥ −2.0 and no other fracture risk factors, BMD and risk status should be

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**Figure 1.** Recommended algorithm for managing bone health in women receiving AI therapy for breast cancer. If patients experience an annual decrease in BMD of ≥10% or ≥4%–5% in patients who were osteopenic at baseline (using the same dual-energy X-ray absorptiometry machine), secondary causes of bone loss such as vitamin D deficiency should be evaluated and antiresorptive therapy initiated. Use lowest T-score from three sites. A Denosumab may be a potential treatment option for some patients. Although ONJ is an uncommon event, rarely observed in the first years of ZOL treatment in the AIBL setting, regular dental care and attention to oral health is advisable in patients receiving bisphosphonates or denosumab. Adapted from Hadji et al. [2]. AI, aromatase inhibitor; AIBL, aromatase inhibitor-associated bone loss; BMD, bone mineral density; BMI, body mass index; ONJ, osteonecrosis of the jaw; ZOL, zoledronic acid.
reassessed after 1–2 years. An annual BMD decrease of ≥10% (or an annual decrease of 4%–5% or more in patients who were osteopenic at baseline) should trigger investigation for secondary causes of bone loss such as vitamin D deficiency, together with antiresorptive therapy. Any patient initiating or receiving AI therapy with any two of the following risk factors should receive antiresorptive therapy: T-score ≤ −1.5, age > 65 years, low BMI (<20 kg/m²), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use of >6 months, and current or history of smoking. Any patient initiating or receiving AI therapy with a T-score ≤ −2.0 should receive antiresorptive therapy. Therefore, as long as antiresorptive therapy to prevent additional bone loss is promptly initiated, established osteoporosis is not a contraindication for AI therapy in postmenopausal women with EBC. Based on current evidence, i.v. ZOL (4 mg q6mo) is the preferred agent for preventing and treating AIBL; however, alternate treatments (oral bisphosphonates or denosumab) may be considered for individual patients. The advantages and limitations of the different antiresorptive therapies investigated in the AIBL setting are summarized in Table 3.

In all patients receiving oral bisphosphonate therapy, BMD should be monitored and compliance should be assessed every 1–2 years. As suggested in our original guidance, periodic assessment of bone resorption marker levels may offer a convenient, noninvasive, but objective measure of compliance with therapy [2]. In case of poor compliance or unsatisfactory BMD improvements after 1–2 years, a switch to i.v. bisphosphonate is recommended. For patients receiving i.v. bisphosphonates or other agents administered by health care providers, BMD monitoring during therapy should be carried out on an individualized basis.

Patients receiving AIs are at elevated risk of fracture for at least the duration of AI treatment [9]. As a result, we recommend continuing antiresorptive therapy for as long as the patient is receiving an AI (up to 5 years). Currently, ZOL is the only antiresorptive agent with proven efficacy and safety over such a long duration—the Z-FAST and ZO-FAST studies have completed 61 and 36 months follow-up, respectively, and demonstrate the continued efficacy and safety of twice-yearly ZOL in preventing AIBL [28, 39]. Long-term safety and efficacy data for other agents (oral bisphosphonates and denosumab) in this specific setting are emerging. Consequently, side-effect profiles and management should be taken into account when selecting an antiresorptive agent to prevent or treat AIBL.

**Conclusions and future directions**

It is now evident that, in addition to BMD, clinical risk factors can greatly influence fracture risk. In addition to morbidity and mortality, fractures are associated with high health care costs and increased health care utilization for several months after fracture incidence [69–71]. Typically, hip and vertebral fractures are associated with the highest direct treatment costs (up to $36 000 per incident on average [69]) and are likely to result in prolonged disability and lack of autonomy, thereby leading to increased indirect costs. Improvements in assessing fracture risk can help identify patients who need pharmacologic intervention to improve bone health, which could help reduce fracture incidence. We have presented an evidence-based algorithm for assessing bone health and initiating antiresorptive therapy in postmenopausal women initiating AI therapy for early-stage breast cancer. Based on the strength of current evidence, we recommend twice-yearly ZOL for up to 5 years for preventing AIBL in postmenopausal women receiving adjuvant AI therapy. Although the trials of adjuvant ZOL were not powered to detect significant between-group differences in fracture rates, additional follow-up may provide insight regarding the effects of treatment on long-term fracture incidence. However, off-study use of bisphosphonates may

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**Table 3. Comparison of antiresorptive agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Long-term safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bisphosphonates</td>
<td>• Oral (self) administration</td>
<td>• Limited efficacy data available in AIBL setting</td>
<td>• Established in the osteoporosis setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Need to follow strict dosing guidelines</td>
<td>• Generally well tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poor compliance and persistence</td>
<td></td>
</tr>
<tr>
<td>Intravenous bisphosphonates</td>
<td>• Efficacy data from large trials with 2–5 years follow-up</td>
<td>• Intravenous administration by health care provider</td>
<td>• Need further follow-up in the osteoporosis (yearly) and AIBL (biannual) settings</td>
</tr>
<tr>
<td>(zolendronic acid)</td>
<td>• Can be administered during routine twice-yearly oncologist visits</td>
<td></td>
<td>• Generally well tolerated</td>
</tr>
<tr>
<td>Denosumab</td>
<td>• Compliance can be ensured</td>
<td>• Limited efficacy data available in AIBL setting</td>
<td>• Not yet known</td>
</tr>
<tr>
<td></td>
<td>• Can be administered during routine twice-yearly oncologist visits</td>
<td>• Subcutaneous administration by health care provider</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Compliance can be ensured</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AIBL, aromatase inhibitor-associated bone loss.
confound interpretation of these data. In addition, although not currently available, future cost-effectiveness analyses will likely influence health care authorities’ treatment decisions in this setting. Long-term efficacy and safety data for ZOL and other agents continue to mature and should be taken into consideration as they become available; none the less, other agents may be reasonable alternatives for some patients.

In addition to the established risk factors used in our bone health algorithm, other potential fracture risk factors in women with breast cancer include low weight and family history of non-hip fractures [36]. An additional potential risk factor is excessive alcohol consumption [72]. Further studies examining the roles of these factors are warranted. Furthermore, periodic (annual) assessment of breast cancer patients with these potential risk factors may be prudent.

Overall, data from the AIBL setting as well as long-term use to treat postmenopausal osteoporosis indicate that bisphosphonates are safe and effective agents for preserving bone health during adjuvant endocrine therapy for breast cancer. In addition, emerging anticancer benefits (e.g. reduced disease recurrence, improved disease-free survival, and prolonged overall survival) from bisphosphonates provide additional reasons to proactively use these agents during adjuvant AI treatment. Ongoing trials are evaluating the potential of oral and i.v. bisphosphonates and denosumab to prevent breast cancer recurrence. As data from these trials mature, the role of antiresorptive agents in EBC is likely to evolve.

acknowledgements

We thank Shalini Murthy and Michael Hobert, ProEd Communications, Inc., for medical editorial assistance with this manuscript. We are also grateful to Michele Tubiana-Hulin for her contributions in the development of the original recommendations and wish her the very best in retirement.

disclosure

PH has received honoraria and unrestricted educational grants from Amgen, AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Roche, Sanofi-Aventis, and Wyeth. MSA has conducted studies and is a consultant on bisphosphonates for Amgen, Bayer Schering, Novartis, and Roche. JJB has received consultancy fees from Novartis and Amgen and speaker fees from Amgen. REC has received consultancy fees from Novartis, Amgen, and Pfizer; speaker fees from Novartis, Roche, Pfizer, AstraZeneca, and Amgen; and research funding from Novartis and has given expert testimony on their behalf. MG reports receiving research support from and serving as a consultant for AstraZeneca, Novartis, and Pfizer and receiving lecture fees and honoraria for participation on advisory boards from AstraZeneca, Novartis, Sanofi-Aventis, Roche, Schering, Amgen, and Pfizer. TG has participated in speakers’ bureaus/advisory boards for Amgen, Novartis, Lilly, Roche, and AstraZeneca and owns stock in Amgen. AL has participated in speakers’ bureaus for Amgen, Novartis, and Genentech; advisory boards for Amgen, Novartis, Cephalon, and Thar Pharmaceuticals; has received research support from Novartis, Monogram Biosciences, Oncogene Science, and PA Breast Cancer Coalition; and has provided expert testimony for Novartis. NB and AB have declared no conflicts of interest.

references


