Prevention and treatment of side-effects of systemic treatment: bone loss

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Cancer treatment-induced bone loss (CTIBL) is generally more rapid and severe than bone loss associated with menopause in women or ageing in men and women. In premenopausal women with breast cancer, CTIBL is mainly caused by chemotherapy with resultant ovarian failure, by GnRH agonists or by tamoxifen. In postmenopausal women, steroidal and non-steroidal aromatase inhibitors (AIs) increase bone turnover, decrease bone mass and increase fracture rate (hazard ratio increased to 1.38–1.55 compared with tamoxifen). Zoledronic acid can prevent bone loss in premenopausal women receiving adjuvant therapy with goserelin in combination with either anastrozole or tamoxifen and in postmenopausal women receiving AIs. Denosumab has been shown in a placebo-controlled study to significantly increase bone mineral density in postmenopausal women under AIs. More limited studies indicate that oral bisphosphonates used at licensed doses for the treatment of postmenopausal osteoporosis can also prevent AI-induced bone loss. In prostate cancer, bone loss that occurs with androgen deprivation therapy (ADT) also leads to an increased fracture rate. The bisphosphonates pamidronate and alendronate can prevent bone loss whereas zoledronic acid can increase bone mass under ADT. As for breast cancer, delay in bisphosphonate therapy is detrimental to bone health. The protective effects of denosumab on bone loss and incidental vertebral fractures have been demonstrated in a 3-year placebo-controlled trial.

Key words: Bisphosphonate, bone, breast cancer, denosumab, osteoporosis, prostate cancer

The benefits of adjuvant treatment for breast and prostate cancer have been attended by additional potential toxicities related to therapy. Patients with endocrine-related cancers are thus at increased risk of developing osteoporosis as a complication of their anticancer treatment [1, 2]. This article focuses on hormone therapy-induced bone loss in early breast and prostate cancer, but hypoestrogenism due to chemotherapy with resultant ovarian failure can cause marked bone loss as well. Cancer treatment-induced bone loss (CTIBL) can lead to osteoporosis, decreased bone strength and increased fracture risk [2, 3]. Substantial negative effects of osteoporotic fractures have been shown on morbidity, mortality and overall healthcare costs [3]. CTIBL is generally more rapid and severe than bone loss associated with menopause in women or ageing in men and women. Thus, aromatase inhibitor (AI)-associated bone loss occurs at a rate at least 2-fold higher than bone loss seen in healthy, age-matched premenopausal women [4]. Bone mineral density (BMD) measured by densitometry (DXA) has been used as a surrogate for fracture risk in most studies.

breast cancer

increased bone loss and increased fracture rate.

In premenopausal women, CTIBL can be caused by chemotherapy with resultant ovarian failure, by GnRH agonists such as goserelin, or by tamoxifen. Chemotherapy-induced ovarian dysfunction accelerates the onset of menopause by an average of 10 years [5]. A recent study reported the adverse effects on bone of six cycles of doxorubicin–cyclophosphamide in 53 premenopausal women (mean age 38 years). All women became amenorrheic and were evaluated at 6 and 12 months after starting chemotherapy. Mean percentage reductions in BMD were 5.2%, 2.8% and 4.0% at the lumbar spine, femoral neck and total hip, respectively [6]. Within the first 6 months of goserelin treatment, >95% of premenopausal women experience amenorrhea, resulting in loss of both cortical and trabecular bone. In the Zoladex Early Breast Cancer Research Association (ZEBRA) study, assessing the effect of goserelin administration for 2 years with 6-monthly cycles of cyclophosphamide, methotrexate and flurouracil (CMF) adjuvant chemotherapy, mean decreases from baseline BMD were −10.5% for goserelin-treated and −6.5% for CMF-treated patients at the spine (P < 0.001) and −6.4% and −4.5% at the hip, respectively [7]. Lastly, despite acting as a partial estrogen agonist on the skeleton, tamoxifen causes bone loss in premenopausal patients, probably because it has a weaker effect on bone than endogenous estrogens. In a placebo-controlled tamoxifen chemoprevention trial, the mean annual loss in lumbar BMD over the 3-year study period in tamoxifen-treated compliant women who remained premenopausal throughout the study period was 1.4% compared with a small gain of 0.2% per year for women on placebo (P < 0.001). Tamoxifen had the
Table 1. Fracture rates in postmenopausal women with early breast cancer receiving aromatase inhibitors (AIs) compared with tamoxifen (Tam) and in men with early prostate cancer receiving GnRH agonists compared with controls

<table>
<thead>
<tr>
<th>AI/GnRH agonist</th>
<th>Trial</th>
<th>Follow-up, months</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upfront strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole</td>
<td>ATAC</td>
<td>100</td>
<td>1.55 (1.31 to 1.83)</td>
<td>&lt;0.0001</td>
<td>14</td>
</tr>
<tr>
<td>Letrozole</td>
<td>BIG 1-98</td>
<td>60</td>
<td>1.38 (1.13 to 1.69)</td>
<td>0.001</td>
<td>15</td>
</tr>
<tr>
<td>Switch strategy (after 2-3 years of Tam)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>IES</td>
<td>56</td>
<td>1.45 (1.13 to 1.87)</td>
<td>=0.003</td>
<td>16</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRH agonist</td>
<td>Cohort study</td>
<td>12–60</td>
<td>1.21 (1.09 to 1.34)</td>
<td>&lt;0.001</td>
<td>17</td>
</tr>
<tr>
<td>(≥29 doses)</td>
<td>Cohort study</td>
<td>&gt;60</td>
<td>1.45 (1.36 to 1.56)</td>
<td>&lt;0.001</td>
<td>18</td>
</tr>
</tbody>
</table>

CI, confidence interval.

*Median value for breast cancer.
after a median follow-up of 28 months, there were significantly more clinical fractures in patients who switched to anastrozole than in those who continued on tamoxifen, 2% versus 1%, respectively (P < 0.05) [23]. However, in a further survival analysis when 42.5% of the patients had completed the planned 5 years of adjuvant treatment, the percentages of patients who had a fracture were reported to be similar (2.2%). The authors speculate that this apparent absence of deleterious effect was due to the osteoprotective effects of tamoxifen for 2 years before anastrozole therapy [24].

In summary, results of available clinical studies indicate that all three third-generation AIs increase bone turnover, decrease BMD and increase fracture risk.

prevention and treatment of CTIBL in breast cancer

Lifestyle and dietary interventions such as exercise and calcium supplementation may improve overall bone health, but typically are not sufficient to prevent CTIBL. The prevention by bisphosphonates of bone loss associated with chemotherapy-induced menopause has been recently reassessed. Because the rate of BMD loss during chemotherapy is greater than after natural menopause, clinical trials evaluated intravenous bisphosphonates using more frequent dosing compared with the postmenopausal osteoporosis setting (e.g. quarterly instead of annual dosing for zoledronic acid). One hundred and one premenopausal women undergoing adjuvant chemotherapy (four to eight cycles) for early breast cancer were randomized between zoledronic acid (or zoledronate) 4 mg every 3 months versus placebo for 1 year; 62 patients completed the 24-month evaluation. At this time, 61% had not regained their menses. In the placebo group, lumbar spine BMD decreased from baseline by 5.5% at 1 year and by 6.3% at 2 years whereas in zoledronic acid-treated patients, BMD remained stable [25].

The Austrian Breast and Colorectal Cancer Study Group has conducted a 3-year randomized trial (ABC0G-12) to investigate the effects of zoledronic acid (4 mg via 15-min infusion every 6 months) on bone loss in premenopausal women receiving adjuvant therapy with goserelin in combination with either anastrozole or tamoxifen. It was shown in a bone density subprotocol that zoledronic acid could completely prevent accelerated bone loss during 3 years in the anastrozole and in the tamoxifen groups [26]. At 5 years of follow-up, i.e. 2 years after completion of treatment, there was partial recovery of bone loss in patients without zoledronic acid but these patients still had reduced BMD compared with baseline values (~6.3% at the lumbar spine; P = 0.001). In contrast, patients who received zoledronic acid had increased BMD at 5 years (+4.0%; P = 0.02) [27]. Quite importantly, disease-free survival (DFS) was significantly improved for patients who received zoledronic acid in addition to endocrine therapy (HR = 0.643; 95% CI 0.46 to 0.91).

Initiation of bisphosphonate therapy early, before the occurrence of severe osteoporosis or fracture, rather than late, may be more effective to counteract CTIBL. This is supported by the Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST and E-ZO-FAST) in which zoledronic acid was evaluated for prevention of CTIBL in nearly 2200 postmenopausal women with early breast cancer receiving adjuvant letrozole for 5 years. Zoledronic acid (4 mg every 6 months) was administered either up front or delayed (until post-baseline T-score declined to less than −2 SD or occurrence of fracture). At 36 months in the Z-FAST study (North America), the mean change in lumbar spine BMD from baseline was 3.7% in the upfront group (n = 189) and −3.0% in the delayed group (n = 188), resulting in a significant absolute difference of 6.7% between groups (Table 2; P < 0.001). At the hip, the absolute difference was 5.2% between groups (P < 0.001). There was no significant difference between groups for clinical or radiological fracture rate but the trial was not designed to detect a significant difference in the fracture rate between treatment arms [28]. Moreover, the use of delayed zoledronic acid in the control arm decreased the statistical power of these trials for a fracture-prevention end point. The 24-month data of the ZO-FAST trial appear to show an even greater difference in BMD between the immediate and the delayed arms.

Oral bisphosphonates used at licensed doses for the treatment of postmenopausal osteoporosis have also been shown to prevent AI-induced bone loss (Table 2). The ARIBON study includes a double-blind, placebo-controlled trial of ibandronate in 50 osteopenic women taking anastrozole. After 2 years, BMD increased by 3.0% at the lumbar spine and 0.6% at the hip in ibandronate-treated women, whereas patients treated with placebo lost 3.2% at the spine and 3.9% at the hip (P < 0.01 at both sites) [29]. The SABRE trial has similarly evaluated the effects of licensed doses of risedronate for the prevention of anastrozole-induced bone loss in osteopenic women. At 24-month follow-up, a significant difference in the change in BMD was seen in favour of anastrozole + risedronate compared with anastrozole + placebo for the lumbar spine (2.2% versus −1.8%; P < 0.0001) and total hip (1.8% versus −2.6%).

Table 2. Effects of bisphosphonates and denosumab on bone mineral density (BMD) at the lumbar spine (LS) and at the hip in postmenopausal women with early breast cancer receiving AIs and in men with early prostate cancer receiving GnRH agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Duration (years)</th>
<th>Difference in BMD versus placebo, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronate</td>
<td>i.v. (Z-FAST)</td>
<td>3</td>
<td>6.7*</td>
<td>28</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>oral</td>
<td>2</td>
<td>6.2</td>
<td>29</td>
</tr>
<tr>
<td>Risedronate</td>
<td>oral</td>
<td>2</td>
<td>4.0</td>
<td>30</td>
</tr>
<tr>
<td>Denosumab</td>
<td>s.c.</td>
<td>2</td>
<td>7.6</td>
<td>31</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Pamidronate</td>
<td>1</td>
<td>3.8</td>
<td>32</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>i.v.</td>
<td>1</td>
<td>7.3</td>
<td>33</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>i.v.</td>
<td>1</td>
<td>7.1</td>
<td>34</td>
</tr>
<tr>
<td>Alendronate</td>
<td>oral</td>
<td>1</td>
<td>5.1</td>
<td>35</td>
</tr>
<tr>
<td>Denosumabb</td>
<td>s.c.</td>
<td>2</td>
<td>6.6</td>
<td>36</td>
</tr>
</tbody>
</table>

i.v., intravenous; s.c., subcutaneous.
*Early versus delayed treatment.
\(^b\)And decreased incidence of new vertebral fractures.
Bone loss that occurs with androgen deprivation therapy (ADT) is more rapid and severe than that associated with normal age-related bone loss and at least comparable to the rate associated with menopause. In normal men, BMD decreases at a rate of 0.5%–1.0% per year starting in mid-life [37]. ADT reduces BMD by 3%–7% per year [38]. ADT also increases fracture risk and the HRs appear to be comparable to those reported for AIs in breast cancer (Table 1). Oefelein et al. [39] reported that men under ADT were at a 5-fold increased risk of skeletal fractures compared with reported rates in age-matched control subjects. The 5- and 10-year fracture rates were 13% and 33%, respectively. In another retrospective review of 395 patients with a mean follow-up of 66 months, 7% of the patients developed fragility fractures [40]. A large cohort study from a 5% national random sample of Medicare beneficiaries confirmed that ADT increases fracture risk; 3779 men treated with GnRH agonists were compared with men with early prostate cancer who did not receive GnRH agonist treatment (n = 8341) [17]. The clinical fracture rate was 7.91 per 100 person-years at risk among GnRH agonist users as compared with 6.55 per 100 person-years in matched controls (HR 1.21; 95% CI 1.09 to 1.34; P < 0.001). Rates of vertebral fractures (HR 1.18; 95% CI 0.94 to 1.48) and hip fractures (HR 1.76; 95% CI 1.33 to 2.33) were significantly higher in men treated with a GnRH agonist. Treatment-related increases in fracture risk seemed to be restricted to men with at least 1 year of GnRH agonist exposure [17]. Another database study including >50 000 men having received a diagnosis of prostate cancer showed that those who received nine or more doses of GnRH agonists had a relative risk of fracture of 1.45 (95% CI 1.36 to 1.56), which was comparable to the risk observed in the orchidectomy group [18].

Although calcium and vitamin D are recommended, they are not sufficient to prevent ADT-induced bone loss. There are a few randomized studies in patients with prostate cancer demonstrating that the bisphosphonates pamidronate, zoledronic acid and alendronate can prevent bone loss under ADT (Table 2). In a placebo-controlled study, Smith et al. [32] treated 47 patients with locally advanced disease and no evidence of bone metastases with leuprolide alone or in combination with pamidronate 60 mg every 3 months. After 1 year, the control group without bisphosphonates showed a significant decrease in bone mass at the lumbar spine (–3.3%) and at the hip (–1.8%) whereas there were no significant changes in BMD at any skeletal site in the group receiving pamidronate [32]. In a further study, the same group treated 106 men with localized disease at the beginning of ADT either with zoledronic acid 4 mg every 3 months or with placebo infusions. After 1 year, there was a significant reduction in BMD in the placebo group (–2.0%), whereas patients treated with zoledronic acid achieved a significant increase in bone mass at the lumbar spine (5.3%). Mean BMD of the femoral neck, trochanter and total hip also increased in the zoledronic acid group and decreased in the placebo group [33]. However, less frequent dosing might be sufficient. The same group of investigators randomized 40 men with non-metastatic prostate cancer under GnRH agonist therapy between a single 4-mg zoledronic acid infusion and a placebo infusion. All patients had baseline T-scores above –2.5. Duration of ADT differed between groups, 12 ± 16 months (mean ± SE) and 21 ± 17 months, for the zoledronic acid and the placebo groups, respectively. Between-group BMD differences at 12 months were 7.1% (95% CI 4.2% to 10.0%; P < 0.001) at the lumbar spine, 2.6% (0.9% to 4.3%; P < 0.005) at the total hip and 2.1% (–0.1% to 4.4%; P = 0.06) at the femoral neck [34]. The improvement in BMD after a single annual dose of zoledronic acid is thus similar to that reported with quarterly dosing [33]. However, osteoporotic patients were excluded from the more recent trial and patients were on ADT for an average of 1 year, which is different from the initial trial where patients were treated within 1 month of starting ADT. It is currently unclear whether these differences have influenced the results. The greater efficacy of zoledronic acid compared with pamidronate might be explained by the higher potency of zoledronic acid and the relatively low dose of pamidronate (60 mg) used in Smith’s study, in agreement with the fact that bone resorption markers increased before each pamidronate infusion [32]. Oral alendronate is an approved therapy for men with osteoporosis. Greenspan et al. [35] postulated that bone loss due to ADT could also be reversed with the same therapy. They enrolled 112 men with non-metastatic prostate cancer who had been receiving ADT for a median duration of 14 months in a 2-year, double-blind, placebo-controlled, randomized clinical trial. After 1 year of alendronate therapy (70 mg once weekly), bone mass increased significantly by 3.7% at the spine, 1.6% at the femoral neck and 0.7% at the total hip, respectively. In contrast, men on placebo had significant decreases in bone mass of 1.4% at the spine, and 0.7% at both femoral sites [35]. Patients were subjected to a second random assignment between alendronate or placebo for those who initially received active therapy, whereas the patients who received placebo during the first year were switched to alendronate. There was an additional benefit in terms of BMD gains of a second year of alendronate therapy. Interestingly, patients randomly assigned to begin alendronate in the second year experienced improvements in bone mass at the spine and hip that were
significantly less than in patients who initiated alendronate at baseline. This indicates that delay in bisphosphonate therapy is detrimental to bone health [41]. These data also indicate that the bisphosphonate scheme used for the treatment of age-related osteoporosis could also be a valid therapy for bone loss due to ADT. However, ADT duration was different between the zoledronic acid [33] and the alendronate trials [35], which could influence bisphosphonate efficacy. More trials are needed before claiming that classical bisphosphonate schemes to treat age-related osteoporosis are indeed sufficient to counteract CTIBL in prostate cancer.

As BMD alone does not adequately capture fracture risk, clinical fractures constitute a more compelling trial end point than BMD measurements. Toremifene, a selective estrogen receptor modulator (SERM), and denosumab have each been reported to significantly reduce fracture risk among high-risk men receiving ADT. Toremifene was evaluated in a placebo-controlled trial that enrolled 1389 men receiving ADT for prostate cancer and at high risk of fractures due to either age ≥70 years or low BMD. Patients were randomized to 2 years of 80 mg daily of oral toremifene or placebo. Toremifene-treated patients were found to have superior BMD at the lumbar spine, total hip and femoral neck [42]. According to a recent presentation, the toremifene arm experienced a significantly lower incidence of vertebral fractures (2.5% versus 4.9%; AACR meeting 2009). The protective effects of denosumab on bone loss and incidental vertebral fractures have also been tested in a large-scale placebo-controlled trial in the setting of ADT-induced bone loss [36]. 1468 patients were randomized to receive denosumab (60 mg subcutaneously every 6 months) or placebo for 3 years for a total of 6 doses. Patients were at elevated risk of fracture due to a history of osteoporotic fracture, age ≥70 years, or low BMD. As shown in Table 2, at 2 years, BMD of the lumbar spine (the primary end point) had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group (P < 0.001). Denosumab administration led to significant increases in BMD at various skeletal sites (femoral neck, total hip, distal radius). Importantly, patients treated with denosumab had a decreased incidence of new vertebral fractures at 3 years (1.5% versus 3.9% in the placebo group; HR 0.38; 95% CI 0.19 to 0.78; P = 0.006).

**specific recommendations**

Despite the growing recognition of the frequency and the consequences of CTIBL, there are currently no therapies specifically approved for its prevention. It is recommended that all women starting medical castration therapy or AI therapy and all men starting ADT should be assessed for their risk of osteoporosis and undergo BMD measurement by DXA, the most reliable method for assessing BMD [2]. The prevalence of CTIBL in the setting of adjuvant therapy for breast or prostate cancer indicates that all patients should also be monitored for bone loss by DXA every 1–2 years. The role of markers of bone resorption should be further investigated to assess their ability to predict and monitor bone loss in this setting.

Since cancer therapy-associated bone loss is largely preventable, an aggressive approach to preserve bone health should be implemented. Attention should be paid to bone health through lifestyle modifications and to the administration of supplemental vitamin D (2800 IU per day) and calcium to maintain a calcium intake of 1200–1500 mg per day. Bisphosphonate therapy is recommended in osteoporotic patients but also in osteopenic patients if risk factors for fractures are present [2, 4, 20]. Risk factors for osteoporotic fractures include older age, a prior history of fracture after age 50 years, a history of hip fracture in the mother or father, previous or current use of systemic corticosteroids, a low body mass index, premature menopause, current smoking and an excessive intake of alcohol. It must be pointed out that available studies and treatment recommendations are based on prevention of bone loss but that fracture data are available only for denosumab in patients with prostate cancer. The optimal duration of bisphosphonate therapy is unknown. These drugs are not without side-effects and the reader is referred to other reviews for this topic [2, 20, 43, 44]. Bisphosphonates should probably be administered as long as AIs or ADT are continued, although it can be argued that their prolonged inhibitory activity on bone resorption would allow a shorter treatment, especially for intravenous therapy whose duration of evaluation is limited to 3 years. If confirmed, the recent reports of a possible protective effect of zoledronic acid on the recurrence rate in breast cancer will probably lead to a greater use of antiresorptive agents in the adjuvant setting.

**disclosure**

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**references**


