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Review article

Osteoporosis management in patients with breast cancer: EMAS position statement

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ABSTRACT

Aromatase inhibitors (AIs) are the first-line recommended standard of care for postmenopausal estrogen receptor-positive breast cancer. Because they cause a profound suppression of estrogen levels, concerns regarding their potential to increase the risk of fracture were rapidly raised. There is currently a general consensus that a careful baseline evaluation is needed of the risk of fracture in postmenopausal women about to start treatment with AIs but also in all premenopausal women with early disease. Bisphosphonates have been shown in several phase III trials to prevent the bone loss induced by cancer treatment, although no fracture data are available. Even though they do not have regulatory approval for this indication, their use must be discussed with women at high risk of fracture. Accordingly, several guidelines recommend considering treatment in women with a T-score ≤ -2 or those with two or more clinical risk factors. Moreover, recent data suggest that bisphosphonates, especially intravenous zoledronic acid, may have an anticancer effect, in that they reduce bone recurrence as well as extra-skeletal metastasis and breast cancer mortality in postmenopausal women. The anti-RANK ligand antibody denosumab is also emerging as a new adjuvant therapeutic option to prevent AI-induced bone loss. It has been shown to extend the time to first fracture in postmenopausal women treated with AIs. Several issues still need to be addressed regarding the use of these different agents in an adjuvant setting. The purpose of this position statement is to review the literature on antifracture therapy and to discuss the current guidelines for the management of osteoporosis in women with early breast cancer.

Contents

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Breast cancer remains the most frequent cancer in women and its incidence is increasing. However, the mortality rate has stabilized due to the progress made in the treatment of breast cancer over the last decade. In premenopausal women with hormone receptor-positive breast cancer, the goal of adjuvant treatment is to inhibit the impact of estrogen on the breast, either by blocking the estrogen receptors (with the use of tamoxifen) or by suppressing ovarian function (through surgical oophorectomy or treatment with luteinizing hormone-releasing hormone (LHRH) agonist). In postmenopausal women, blocking the estrogen receptors or inhibiting the aromatase-induced synthesis of estrogen are standard treatment options. Different options for endocrine therapy are outlined in the 2016 NCCN Guidelines [1].

Over the last decade, aromatase inhibitors (AIs) have been frequently used to treat postmenopausal women with estrogen receptor-positive tumors. AIs suppress the conversion of androgens to estrogens, and so result in estrogen depletion. They have also been used in association with GnRH agonists in premenopausal women to induce a profound state of estrogen deficiency. Numerous studies have reported an increased rate of bone loss in AI-treated women [2–6], however, which has raised the question of the risk of fracture. Even though this question is still under discussion because most of the phase III trials with AIs have compared the impact of an AI with that of tamoxifen, which is a well known protector against bone loss and fractures, it is currently recommended that women with breast cancer who are about to receive adjuvant hormonal therapy with AIs are screened for osteoporosis. Moreover, extended therapies with AIs are increasingly being used in women at higher risk of long-term recurrence.

Therefore, it is of particular importance (1) to identify the women at higher risk of fracture at baseline and (2) to introduce antifracture interventions in these women at higher risk of fracture. Several trials have demonstrated the ability of bisphosphonates to inhibit AI-induced bone loss, although very few fracture data are available. In addition, some studies suggest a beneficial effect of bisphosphonates in an adjuvant setting in postmenopausal women, reducing the risk of cancer relapse. More recently, the anti-RANK ligand antibody denosumab has been shown to reduce the incidence of fracture in postmenopausal women with early breast cancer treated with AIs [7].

This position statement aims to synthesize the results of clinical trials of antifracture therapy in women with early-stage breast cancer and to discuss the current guidelines for the management of osteoporosis in women with breast cancer. It also examines whether there is an indication for the use of bisphosphonates or denosumab in an adjuvant setting in women with early breast cancer. The bone impact of chemotherapy and the prevention of bone loss associated with chemotherapy-induced menopause will not be discussed here.

1. Prevention of bone loss induced by adjuvant hormonal treatment

1.1. Bisphosphonates

Bisphosphonates are potent anti-resorbing agents which are widely used for their antifracture efficacy in postmenopausal women with osteoporosis. Since the beginning of the 2000s they have been evaluated in women treated with AIs for breast cancer. The earliest studies showed that oral clodronate given at a dose of 1600 mg/day [8] was associated with an increase in both vertebral and femoral bone mineral density (BMD) in postmenopausal women with breast cancer. Several studies have also demonstrated the efficacy of both risedronate and ibandronate in preventing AI-induced bone loss in women with breast cancer, although some of these studies are of limited value due to small sample sizes or inconclusive results [9–14]. In the open study SOOPA [9], risedronate (35 mg once weekly) was shown to increase vertebral BMD (+4.1%) and to prevent femoral bone loss in a small group of osteoporotic women treated with anastrozole. The double-blind IBIS II study recruited 3,864 healthy postmenopausal women at increased risk of breast cancer and randomly allocated them to anastrazole or placebo [14]. Among these participants, 1,410 women were enrolled into a bone sub-study and stratified at baseline according to their lowest T score at the spine or femoral neck. Women with osteopenia were randomised to risedronate or placebo; those with osteoporosis were all given risedronate. In the 150 women with baseline vertebral or femoral osteopenia, at 3 years there was a 1.1% increase in vertebral BMD in the 77 women receiving anastrozole/risedronate versus a 2.6% decrease for the 73 women receiving anastrozole/placebo ($p < 0.0001$). For the total hip, the 3-year mean BMD change for women receiving anastrozole/risedronate was −0.7% (−1.6 to −0.2) versus −3·5% (−4.6 to −2.3) for women receiving anastrozole/placebo ($p = 0.0001$). Women with normal BMD or osteopenia not receiving risedronate, who received anastrozole (310 women), had a significant BMD decrease after 3 years of follow-up compared with women who received placebo (342 women) at the lumbar spine (−4.0% [−4.5 to −3.4] vs −1.2% [−1.7 to −0.7], $p < 0·0001$) and total hip (−4.0% [−4.4 to −3.6] vs −1.8% [−2.1 to −1.4], $p < 0.0001$). At 3 years, in the osteoporotic group the 46 women allocated to anastrozole had a modest BMD increase of 1.2% (−0.1 to −2.6) at the spine compared with a 3.9% (2.6–5.2) increase for the 60 women allocated to placebo ($p = 0.006$). For the total hip, a small increase of 0.3% (−0.9–1.5) was noted for women allocated anastrozole compared with a 1.5% (0.5 to −2.5) increase for women allocated placebo, but the difference was not significant ($p = 0.12$). Similar results were observed in the SABRE [12] and ARBI [13] studies. In the ARIBON study [10], the 50 women treated with ibandronate in combination with anastrozole showed positive BMD changes when compared with those who were given anastrozole alone (+3% vs −3.2% at the spine and +0.6% vs −3.9% at the hip).

In a more compelling way, several studies have evaluated the effect of zoledronic acid in different treatment settings [15–20]. The first trials (Z-FAST, ZO-FAST) evaluated the effect of zoledronic acid at a dose of 4 mg IV every 6 months given to postmenopausal women treated with letrozole either from the beginning of AI treatment (upfront arm) or as delayed therapy in the case of fracture or in women who had a T-score <−2 over the follow-up [5]. Five years of follow-up were available [18]. In both studies, vertebral and femoral BMD was significantly increased after 3 years of concurrent treatment with letrozole and zoledronic acid in the upfront arms. The overall differences in vertebral BMD were 6.7% and 9.3% at 3 years in the Z-FAST and ZO-FAST trials, respectively, in favour of the groups treated with zoledronic acid. Similar results were observed after 5 years of follow-up [20].

In the NO3CC trial [21], 551 women who were undergoing letrozole treatment after having completed a tamoxifen sequence of treatment were randomly assigned to either upfront or delayed zoledronic acid. All women at baseline had a T-score >−2 and no history of osteoporotic fracture. After 5 years of treatment, a 5% decrease in vertebral BMD was observed in 10.2% of the women in the upfront arm and in 40.2% in the delayed treatment arm ($p < 0.001$). Bone fractures occurred in 24 patients in the upfront arm versus 25 patients in the delayed treatment arm, which was not significantly different.

In an open-label, single-arm observational study, 60 postmenopausal women with hormone receptor-positive breast cancer and osteopenia or osteoporosis (T-score <−2) were prescribed letrozole and zoledronic acid 4 mg IV every 6 months until disease progression (death or development of metastasis in the course of the study) or for a maximum of 5 years. After 5 years, mean BMD had increased by 11.6% at the lumbar spine, a significant difference ($p = 0.01$), and by 4.2% at the femoral neck, although this was not significant. A total of 6 fractures were observed after 417 individual assessments [22].

The ability of zoledronic acid to prevent bone loss has also been shown in premenopausal women receiving adjuvant hormonotherapy and/or chemotherapy [23–26]. In the ABCSG12 trial [23,24], 1,803 non-menopausal women with estrogen receptor-positive early-stage (I/II) breast cancer receiving a GnRH agonist were randomised to receive either anastrozole 1 mg/day or tamoxifen 20 mg/day with or without zoledronic acid (4 mg IV every 6 months) for 3 years. In this open-label randomised study, administration of zoledronic acid in combination of either of the two adjuvant hormonal treatments resulted in a significantly higher BMD when compared with that observed in women who did not receive the bisphosphonates; indeed, the latter group experienced both vertebral and femoral significant bone loss. In the ProBONE II study [25,26], 70 premenopausal women with early-stage breast cancer received adjuvant chemotherapy and/or endocrine therapy plus zoledronic acid (4 mg IV every 3 months) or placebo for 24 months. Lumbar spine BMD increased 3.14% from baseline to 24 months in the women treated with zoledronic acid versus a 6.43% decrease in placebo-treated women ($p < 0.0001$). Similar results were observed in Korean early postmenopausal women with breast cancer treated with an AI alone or in combination with zoledronic acid [27].

Overall, bisphosphonates appear to prevent AI-induced bone loss. Most data have been obtained with zoledronic acid, across different settings and treatment schedules, namely 4 mg IV every 3 or 6 months. Data are less robust for oral bisphosphonates, although observational studies in clinical settings have shown that oral bisphosphonates given at the licensed anti-osteoporotic doses are able to prevent AI-induced bone loss and could thus be a therapeutic option [28]. In any case, no fracture data are available, mostly due to a lack of power in the studies. Moreover, it must be kept in mind that the incidence of fracture is modest in women with breast cancer, at least over a 5-year period of treatment with AIs [29–31].

Administration of bisphosphonates is well tolerated, with few adverse effects (bone pain, arthralgia, asthenia, pyrexia). Osteonecrosis of the jaw is usually not a concern, although the incidence might increase with the frequency of administration and the duration of treatment.

1.2. Denosumab

Denosumab is a fully human monoclonal antibody directed against the receptor activator of the nuclear factor kappa-B (RANK) ligand; it has been licensed for the prevention of fracture in patients with osteoporosis.

In the first study investigating the protective effect of denosumab against AI-induced bone loss, 252 women with early-stage breast cancer undergoing adjuvant AI treatment were randomly assigned to receive denosumab 60 mg or a placebo subcutaneously every 6 months for 2 years [32,33]. At 24 months, lumbar spine BMD and total femoral BMD had increased by 7.6% and 4.7%, respectively, in the denosumab group versus the placebo group. Similar increases in vertebral and hip BMD were seen whatever the nature of AI therapy (non-steroidal and steroidal). The overall incidence of adverse events was similar in the two groups and most commonly included arthralgia, pain in the arms or legs, back pain, and fatigue.

The ABCSG-18 trial [7] was a prospective double-blind placebo-controlled phase 3 study in which postmenopausal women with hormone receptor-positive breast cancer receiving adjuvant AI were randomised to receive either denosumab 60 mg or placebo subcutaneously every 6 months. The primary endpoint was time from randomization until the date of the first fracture. Of the women randomised, 76% (n = 2,579) completed the treatment. At 36 months after randomization, an estimated 5% of patients in the denosumab group had experienced a fracture compared with 9.6% in the placebo group (65 fractures in the denosumab group versus 129 fractures in the placebo group). Among women receiving denosumab, BMD at the lumbar spine was 10% greater than it was among women receiving placebo, and at the femoral neck it was 6.5% greater ($p < 0.0001$). Very surprisingly, the prevention of fracture with denosumab was independent of baseline vertebral T-score; that is, the effect was observed at the same magnitude both in women with a T-score ≥−1 and in women with a T-score <−1. Moreover, it must be noted that the incidence of fracture was about the same in the placebo group whatever the baseline vertebral T-score value (10.8% in women with a baseline T-score <−1 vs 9.85% in women with a baseline T-score ≥−1 over the 7-year period of follow-up), which is quite unusual. Most fractures occurred at the lower forearm, followed by vertebrae, ribs and lower leg. All fractures were recorded, including those after moderate to high trauma, although the reduction in the incidence of fracture in the denosumab group was about the same when only low-trauma fractures were considered. Adverse effects did not differ between the two groups. 31 potential dental problems were further assessed, although no case was judged to meet the diagnostic criteria for osteonecrosis of the jaw. No atypical femoral fracture was recorded.

2. Use of bone anti-resorbing agents in an adjuvant setting in women with early breast cancer

Bone is a highly vascularized organ that contains a hematopoietic niche which is likely to represent a sanctuary for cancer stem cells. Moreover, bone marrow produces a large number of growth factors and cytokines that facilitate cancer cell survival and proliferation. Also, growth factors and cytokines are released by bone cells during the bone-remodeling process, which may enhance metas-

tasis development by stimulating the proliferation of cancer cells [34]. Therefore the interaction between bone and the bone marrow micro-environment plays a major role in the metastasis processes, both within and, potentially at least, also outside bone. This 'seed and soil' concept was developed more than 100 years ago. There is a self-sustaining vicious cycle, with multidirectional interactions between cancer cells, bone cells and the bone micro-environment [35]. Because both bisphosphonates and denosumab have a potent bone anti-resorbing effect, their use for the prevention of bone loss in women with breast cancer is complicated by oncologic issues related to the prevention of bone metastasis and overall survival.

2.1. Breast-cancer adjuvant therapy with bisphosphonates

There are two classes of bisphosphonates, non-nitrogen-containing and nitrogen-containing, and these have different degrees of bone-resorbing activity. Nitrogen-containing bisphosphonates (pamidronate, risedronate, ibandronate, alendronate, zoledronic acid) are more potent osteoclast inhibitors than non-nitrogen-containing bisphosphonates (clodronate, etidronate, tiludronate). Moreover, among nitrogen-containing bisphosphonates, the biochemical structure of the side chains linked to the central carbon chain provides the different bisphosphonates with their affinity for hydroxyapatite and their relative potency. Because of their high affinity for bone mineral, nitrogen-containing bisphosphonates quickly localize to the skeleton, primarily at active remodeling sites. They act through the inhibition of osteoclast-mediated bone resorption, thus alleviating the tumor-associated bone destruction. There is extensive preclinical evidence suggesting that nitrogen-containing bisphosphonates have antitumor effects, although their precise mechanisms of action remain unclear. The main mechanism of action is thought to be inhibition of osteoclast activity through inhibition of the mevalonate pathway. The nitrogen-containing side chain interacts with farnesyl pyrophosphate synthase, which is a key enzyme in the mevalonate pathway, thereby blocking the activity of this enzyme. This leads to the inhibition of prenylation of regulatory small GTPase proteins, which are key components for osteoclast cell functions and proliferation but also multiple other cell systems. Therefore, inhibition of the mevalonate pathway may have an effect on cell functions that goes well beyond inhibition of bone resorption. In addition, nitrogen-containing bisphosphonates exert direct antitumor effects in vitro by inhibiting cell adhesion, migration and proliferation and inducing apoptosis. They may also act indirectly on tumor cells through antiangiogenic and immunomodulatory mechanisms [for review, see Ref. [36]].

Several studies have evaluated the impact of adjuvant bisphosphonates on disease-free survival (DFS) and overall survival (OS), with conflicting results. The earliest studies evaluated the anticancer activity of clodronate in women with early-stage breast cancer. Three trials [8,37,38] were conducted with oral clodronate at the dose of 1600 mg/day over 2–3 years. The trial by Saarto et al. [8] failed to find any significant clinical benefit of clodronate given to 299 women with early-stage breast cancer. The 2 other trials [37,38] suggested that 2 years of clodronate can delay bone metastasis and improve DFS and OS in women with breast cancer. Differences in primary outcomes between the 3 trials may be due to heterogeneity in the study populations, given that they included both premenopausal and postmenopausal women of different hormonal status or different adjuvant anticancer treatment protocols. The issue of endocrine status might represent a particular concern, since some data suggest that the positive impact of bisphosphonates on disease progression might be more pronounced in a low-estrogen environment. The NSABP B-34 double-blind randomised trial [39] evaluated the effect of clodronate (1600 mg/day for 3 years) in 3,233 women with early-stage (II/III) breast cancer. No differences were recorded for DFS (0.91 [CI 95% 0.78–1.07]; p = 0.27) and OS (0.84 [0.67–1.15]; p = 0.13) or non-bone metastasis-free interval. However, when only women older than 50 years were considered, clodronate was associated with a longer recurrence-free interval (0.75 [0.57–0.99]; p = 0.045), bone and non-bone metastasis-free intervals, but not with OS (0.80 [0.61–1.04], p = 0.094).

Several large trials have investigated the potential of adjuvant zoledronic acid to prevent recurrence of breast cancer. In ABCSG-12 [22,24], adding zoledronic acid (4 mg every 6 months for 3 years) to adjuvant therapy (tamoxifen or anastrozole) significantly prolonged DFS both at 48 months (HR = 0.64, p = 0.01) and at 62 months (HR = 0.68, p = 0.009). The final analysis after a median follow-up of 95 months [24] confirmed the beneficial impact of zoledronic acid on DFS and the improvement in OS. Although most patients were still alive after more than 6 years of follow-up, there were fewer deaths among the women who were given zoledronic acid (HR = 0.66 [0.43–1.02]; p = 0.064). Overall, 251 DFS events (generally consistent with known safety profiles of each agent) and 86 deaths were reported. Absolute risk reductions with zoledronic acid were 3.4% for DFS and 2.2% for OS. The anti-cancer effects of zoledronic acid were also observed in the Z-FAST and ZO-FAST studies [17,18]. There was a significant reduction in disease recurrence both in women in the upfront and in women in the delayed zoledronic acid arms, although DFS was significantly improved in the upfront as compared with the delayed arm (HR = 0.59, p = 0.03). On the other hand, in the AZURE trial [40], which was specifically designed to examine the adjuvant impact of zoledronic acid given at a higher dose than in most other trials, in a group of 3,360 premenopausal and postmenopausal women with breast cancer, there were no statistically significant difference in DFS or OS for zoledronic acid compared with controls. However, when only postmenopausal women with more than 5 years since menopause were considered, zoledronic acid improved both DFS (HR = 0.76, p = 0.05) and OS (HR = 0.71, p = 0.17).

Recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of individual patient data for 18,766 participants in 26 randomised trials evaluating the adjuvant use of bisphosphonates in breast cancer [41]. Overall, the addition of adjuvant bisphosphonates was associated with a significant reduction in the 10-year risk of bone recurrence (7.8% versus 9.0%). Although the authors observed reductions at 10 years for distant recurrence (20.4% versus 21.8%), and breast cancer mortality (16.6% versus 18.4%), these differences were of borderline statistical significance. Among the 11,767 postmenopausal women included in the analysis, the use of bisphosphonates was associated with statistically significant reductions in distant recurrence, bone recurrence and death from breast cancer. This again suggested that the anticancer effect of zoledronic acid might be more pronounced in a low-estrogen environment.

Several trials of bisphosphonates are currently ongoing (SWOG0307, SUCCESS trial) and additional data are still needed before the systematic use of adjuvant bisphosphonates in women with early breast cancer can be recommended.

2.2. Breast-cancer adjuvant therapy with denosumab

A combined analysis of three phase III trials [42] in over 5,700 patients with advanced cancer with bone metastasis (including breast, prostate cancer, other solid tumors or multiple myeloma) showed that RANKL inhibition with denosumab at high doses (120 mg sc every 4 weeks) had greater efficacy in the prevention of skeletal-related events (SREs) in patients with bone metastases than did zoledronic acid (4 mg IV every 4 weeks). The risk of the first on-study SRE was reduced by 17% (p < 0.001) in denosumab-treated patients compared with zoledronic acid. The median time

to first on-study SRE was 27.66 months for denosumab versus 19.45 months for zoledronic acid (a difference of 8.21 months). Osteonecrosis of the jaw occurred at a similar rate (n = 52 (1.8%) in the denosumab group vs n = 37 (1.3%) in the zoledronic acid group).

Whether denosumab has an anticancer effect in the adjuvant setting in women with early-stage breast cancer is still under discussion. Survival data from the ABCSG-18 trial and from the D-CARE trial of a higher dose of denosumab should soon be available and will provide information as to whether denosumab might become a valuable additional approach to current treatments.

3. Current guidelines for the management of osteoporosis in women with breast cancer

There is currently no doubt that every woman who is diagnosed with breast cancer should be evaluated for her baseline risk of fracture. Assessment of the risk of fracture includes a full evaluation of the clinical risk factors for fracture and DXA measurement [43]. Blood sampling for calcium metabolism evaluation, including determination of parathyroid hormone (PTH) and 25-hydroxyvitamin D levels, is recommended. Vitamin D deficiency is very frequent in women being treated for breast cancer [44].

Several societies have issued guidelines or recommendations addressing the issue of fracture in women being treated for breast cancer, especially those receiving AI therapy [45–50]. A European panel of leading experts in the field of breast cancer management published a consensus guide in March 2016 on the use of adjuvant bisphosphonates in the prevention of both treatment-induced bone loss and metastasis [51]. Their recommendations for the prevention of osteoporosis and fracture are somewhat comparable to those already published by several societies and working groups. They include both lifestyle recommendations and pharmacological intervention. Calcium supplementation (1000 mg per day) is recommended if dietary intake is insufficient. Also, vitamin D supplementation (800–1000 IU/day) should be discussed in most women with breast cancer. In addition, all patients at risk should be advised to take regular weight-bearing exercise and reduce smoking and alcohol consumption. Anti-resorptive therapies are recommended in women at an increased risk of fracture. However, it must be highlighted that there are still uncertainties regarding how to address the risk of fracture according to menopausal status or the rate of bone loss. In particular, the current guidelines for the evaluation of the risk of fracture in postmenopausal women do not necessarily apply to premenopausal women about to be treated for breast cancer. Similarly, the FRAX score, which has been proposed as a reliable tool to assess the risk of fracture in healthy women, does not include anti-cancer treatment as a specific risk factor and thus its value in determining the risk of fracture in women with breast cancer has not been evaluated. In addition, it is not known how the rate of bone loss or changes in the bone resorption markers which are observed with anti-cancer treatments correlate with the risk of fracture in either premenopausal or postmenopausal women.

Most guidelines, including the most recent guidance from the European panel, recommend that all women with a T-score ≤ -2 or those with two or more clinical risk factors for fracture should be treated. Bisphosphonates are the therapies of choice to prevent the bone loss induced by cancer treatment. To date, there is no recommendation regarding the use of denosumab in women with early-stage breast cancer, although it has been shown to prevent bone loss and extend the time to first fracture in postmenopausal treated with AIs [7]. Several issues still need to be examined regarding the duration of treatment since discontinuation of denosumab has been associated with transient increases in bone remodeling and rapid bone loss [52]. There are, moreover, some concerns that discontinuation of therapy might also enhance the proliferation of dormant cancer cells.

In premenopausal women, zoledronic acid should be preferred, since it is the only bisphosphonate which has been shown to prevent the bone loss associated with goserelin + tamoxifen/anastrozole [24] or with chemotherapy-induced ovarian failure [53]. In postmenopausal women, oral bisphosphonates or IV zoledronic acid, whatever the regimen, including anti-osteoporotic doses, are effective in reducing AI-induced bone loss. In any case, it must be pointed out that there are no fracture data with the use of bisphosphonates in women with early breast cancer.

The use of adjuvant bisphosphonates to prevent metastasis or to improve disease outcomes was also examined by the European panel [51]. They suggest that bisphosphonates could be considered in women at intermediate to high risk of recurrence, especially postmenopausal women, although there is a lack of regulatory approval in this setting. The data suggest that menopausal status at the time of administration of adjuvant bisphosphonates is important. The findings reported by the Early Breast Cancer Trialists' Collaborative Group [41] suggested that bisphosphonates not only decrease rates of recurrence in bone but also overall breast cancer recurrence rates and breast cancer mortality in postmenopausal women. Either daily oral clodronate or IV zoledronic acid (every 6 months) is the preferred agent for metastasis prevention. The duration of treatment remains unclear, although a 3–5-year period has been proposed [51]. The expected beneficial disease outcomes of such interventions must be balanced against the risk of osteonecrosis of the jaw (1.7% in the AZURE trial [40]) and of acute renal failure.

4. Summary

Because women with breast cancer can now expect to live longer than before, the prevention of morbidity induced by the cancer treatment should be a concern. AIs are associated with an increased risk of bone loss, although there are still questions regarding the risk of fracture associated with AIs when they are used in the treatment of postmenopausal women with early breast cancer. A careful baseline evaluation of the risk of fracture is recommended in all premenopausal women with breast cancer and in postmenopausal women about to start treatment with an AI. A pharmacological intervention is recommended for women with a T-score ≤ -2 or those with two or more clinical risk factors for fracture, alongside vitamin D supplementation and adequate calcium intake. There is a consensus that bisphosphonates should be used to prevent the bone loss induced by cancer treatment, especially in women at intermediate or high risk of fracture. The use of denosumab could also be considered, although there is currently no specific guideline regarding this agent. Osteoporotic treatment should be continued at least until the adjuvant breast cancer treatment programme is complete, or even longer in those women with the highest baseline risk of fracture. Exciting perspectives regarding the use of bisphosphonates (particularly IV zoledronic acid) in improving long-term health outcomes in women with early breast cancer are now emerging. Although the use of bisphosphonates in such settings has not been considered by most regulatory agencies, there are strong data to support the use of adjuvant bisphosphonates in postmenopausal women for metastasis prevention, after careful consideration of the potential benefits and risks. Several issues still need to be addressed concerning the regimen and duration of treatment. Ongoing adjuvant trials should provide further information on the use of adjuvant therapies in women with breast cancer.

Contributors

Florence Tremollieres prepared the initial draft, which was circulated to EMAS board members for comment and approval; production was coordinated by Irene Lambrinoudaki and Margaret Rees.

Conflict of interest

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References

[1] W. Gradishar, K.E. Salerno, NCCN guidelines update: breast cancer, J. Natl. Compr. Canc. Netw. 14 (Suppl. 5) (2016) 641–644, May.
[2] R. Eastell, R.A. Hannon, J. Cuzick, et al., Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the anastrozole, tamoxifen, alone or in combination (ATAC) trial (18233230), J. Bone Miner. Res. 21 (2006) 1215–1223.
[3] R.E. Coleman, L.M. Banks, S.I. Girgis, et al., Skeletal effects of exemestane on bone mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the intergroup exemestane study (IES): a randomised controlled study, Lancet Oncol. 8 (2007) 119–127.
[4] P.E. Goss, J.N. Ingle, S. Martino, et al., Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17, J. Natl. Cancer Inst. 97 (2005) 1262–1271.
[5] S. Gonnelli, A. Cadirni, C. Caffarelli, et al., Changes in bone turnover and in bone mass in women with breast cancer switched from tamoxifen to exemestane, Bone 40 (2007) 205–210.
[6] P. Hadji, M. Ziller, D.G. Kieback, et al., Effects of exemestane and tamoxifen on bone health within the tamoxifen exemestane adjuvant multicentre (TEAM) trial: results of a German, 12-month, prospective, randomised substudy, Ann. Oncol. 20 (2009) 1203–1209.
[7] M. Gnant, G. Pfeiler, P.C. Dubsky, et al., Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial, Lancet 386 (2015) 433–443.
[8] T. Saarto, L. Vehmanen, I. Elomaa, et al., The effect of clodronate and antioestrogens on bone loss associated with oestrogen withdrawal in postmenopausal women with breast cancer, Br. J. Cancer 84 (2001) 1047–1051.
[9] C.B. Confavreux, A. Fontana, J.P. Guastalla, F. Munoz, J. Brun, P.D. Delmas, Estrogen-dependent increase in bone turnover and bone loss in postmenopausal women with breast cancer treated with anastrozole. Prevention with bisphosphonates, Bone 41 (2007) 346–352.
[10] J.E. Lester, D. Dodwell, O.P. Purohit, et al., Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer, Clin. Cancer Res. 14 (2008) 6336–6342.
[11] S.L. Hines, B.A. Mincey, J.A. Sloan, et al., Phase III randomised, placebo-controlled double-blind trial of risedronate for the prevention of bone loss in premenopausal women undergoing chemotherapy for primary breast cancer, J. Clin. Oncol. 27 (2009) 1047–1053.
[12] C. Van Poznak, R.A. Hannon, J.R. Mackey, et al., Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial, J. Clin. Oncol. 28 (2010) 967–975.
[13] C. Markopoulos, E. Tzoracoleftherakis, A. Polychronis, et al., Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial, Breast Cancer Res. 12 (2010) R24.
[14] I. Sestak, S. Singh, J. Cuzick, et al., Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial, Lancet Oncol. 15 (2014) 1460–1468.
[15] A. Brufsky, W.G. Harker, J.T. Beck, et al., Zoledronic acid inhibits adjuvant letrozole induced bone loss in postmenopausal women with early breast cancer, J. Clin. Oncol. 25 (2007) 829–836.
[16] N.J. Bundred, I.D. Campbell, N. Davidson, et al., Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST study results, Cancer 112 (2008) 1001–1010.
[17] H. Eidtman, R. de Boer, N. Bundred, et al., Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST study, Ann. Oncol. 21 (2010) 2188–2194.
[18] A. Brufsky, W.G. Harker, J.T. Beck, et al., Final 5-year results of Z-FAST trial adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole, Cancer 118 (2012) 1192–1201.
[19] A. Llombart, A. Frassoldati, O. Paija, et al., Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial, Clin. Breast Cancer 12 (2012) 40–48.
[20] R. Coleman, R. de Boer, H. Eidtmann, et al., Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results, Ann. Oncol. 24 (2013) 398–405.
[21] N.D. Wagner-Johnston, J.A. Sloan, H. Liu, et al., 5-year follow-up of a randomised controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (alliance) trial, Cancer 121 (2015) 2537–2543.
[22] N. Majithia, P.J. Atherton, J.M. Lafky, N. Wagner-Johnston, J. Olson, S.R. Dakhil, E.A. Perez, C.L. Loprinzi, S.L. Hines, Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy: a 5-year follow-up, Support. Care Cancer 24 (2016) 1219–1226.
[23] M. Gnant, B. Mlineritsch, G. Luschin-Ebengreuth, et al., Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy, Lancet Oncol. 9 (2008) 840–849.
[24] M. Gnant, B. Mlineritsch, H. Stoeger, et al., Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozole plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian breast and colorectal cancer study group trial 12, Ann. Oncol. 26 (2015) 313–320.
[25] P. Hadji, A. Kauka, M. Ziller, et al., Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: the ProBONE II study, Osteoporos. Int. 25 (2014) 1369–1378.
[26] M. Kalder, I. Kyvernitakis, U.S. Albert, M. Baier-Ebert, P. Hadji, Effects of zoledronic acid versus placebo on bone mineral density and bone texture analysis assessed by the trabecular bone score in premenopausal women with breast cancer treatment-induced bone loss: results of the ProBONE II substudy, Osteoporos. Int. 26 (2015) 353–360.
[27] S.A. Lee, S.H. Hwang, S.G. Ahn, et al., Effects of zoledronic acid on bone mineral density during aromatase inhibitor treatment of Korean postmenopausal breast cancer patients, Breast Cancer Res. Treat. 130 (2011) 863–870.
[28] B. Bouvard, P. Soulié, E. Hoppé, et al., Fracture incidence after 3 years of aromatase inhibitor therapy, Ann. Oncol. 25 (2014) 843–847.
[29] Z. Chen, M. Maricic, T.L. Bassford, et al., Fracture risk among breast cancer survivors: results from the women's health initiative observational study, Arch. Intern. Med. 165 (2005) 552–558.
[30] A.L. Cooke, C. Metge, L. Lix, H.J. Prior, W.D. Leslie, Tamoxifen use and osteoporotic fracture risk: a population-based analysis, J. Clin. Oncol. 26 (2008) 5227–5232.
[31] P. Vestergaard, L. Rejnmark, L. Mosekilde, Fracture risk in patients with different types of cancer, Acta Oncol. 48 (2009) 105–115.
[32] G.K. Ellis, H.G. Bone, R. Chlebowski, et al., Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non metastatic breast cancer, J. Clin. Oncol. 26 (2008) 4875–4882.
[33] G.K. Ellis, H.G. Bone, R. Chlebowski, et al., Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study, Breast Cancer Res. Treat. 118 (2009) 81–87.
[34] M.B. Meads, L.A. Hazlehurst, W.S. Dalton, The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance, Clin. Cancer Res. 14 (2008) 2519–2526.

[35] S. Paget, The distribution of secondary growths in cancer of the breast, Lancet 133 (1889) 571–573.
[36] M. Gnant, P. Clezardin, Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature, Cancer Treat. Rev. 38 (2012) 407–415.
[37] I.J. Diel, E.F. Solomayer, S.D. Costa, et al., Reduction in new metastases in breast cancer with adjuvant clodronate treatment, N. Engl. J. Med. 339 (1998) 357–363.
[38] T. Powles, A. Paterson, E. McCloskey, et al., Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026], Breast Cancer Res. 8 (2006) R13.
[39] A.H.G. Paterson, S.J. Anderson, B.C. Lembersky, et al., Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel project protocol B-34): a multicentre, placebo-controlled, randomised trial, Lancet Oncol. 13 (2012) 734–742.
[40] R.E. Coleman, H. Marshall, D. Cameron, et al., Breast-cancer adjuvant therapy with zoledronic acid, N. Engl. J. Med. 365 (2011) 1396–1405.
[41] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 386 (2015) 1353–1361.
[42] A. Lipton, K. Fizazi, A.T. Stopeck, et al., Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials, Eur. J. Cancer 48 (2012) 3082–3092.
[43] F.A. Tremollieres, Screening for osteoporosis after breast cancer: for whom, why and when, Maturitas 79 (2014) 343–348.
[44] B. Bouvard, E. Hoppé, P. Soulié, et al., High prevalence of vertebral fractures in women with breast cancer starting aromatase inhibitor therapy, Ann. Oncol. 23 (2012) 1151–1156.
[45] H.J. Burstein, A.A. Prestrud, J. Seidenfeld, American society of clinical oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer, J. Clin. Oncol. 28 (2010) 3784–3796.
[46] P. Hadji, J.J. Body, M.S. Aapro, et al., Practical guidance for the management of aromatase inhibitor-associated bone loss, Ann. Oncol. 19 (2008) 1407–1416.
[47] P. Hadji, M.S. Aapro, J.J. Body, et al., Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment, Ann. Oncol. 22 (2011) 2546–2555.
[48] D.M. Reid, J. Doughty, R. Eastell, et al., Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group, Cancer Treat. Rev. 34 (S1) (2008) S3–18.
[49] R. Rizzoli, J.J. Body, A. De Censi, et al., Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper, Osteoporos. Int. 23 (2012) 2567–2576.
[50] R. Coleman, J.J. Body, M. Aapro, et al., Bone health in cancer patients: ESMO clinical practice guidelines, Ann. Oncol. 25 (S3) (2014) 125–137.
[51] P. Hadji, R.E. Coleman, C. Wilson, et al., Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European panel, Ann. Oncol. 27 (2016) 379–390.
[52] S. Boonen, S. Ferrari, P.D. Miller, et al., Postmenopausal osteoporosis treatment with antiresorptives: effects of discontinuation or long-term continuation on bone turnover and fracture risk—a perspective, J. Bone Miner. Res. 27 (2012) 963–974.
[53] C.L. Shapiro, S. Halabi, V. Hars, et al., Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809, Eur. J. Cancer 47 (2011) 683–689.