Maturitas xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Skeletal health in breast cancer survivors

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ARTICLE INFO

Keywords:
Skeletal health
Breast cancer
Survivors

ABSTRACT

Although some risk factors for breast cancer might be protective for osteoporosis, several cross-sectional studies have reported, nevertheless, that patients with breast cancer have a lower bone mass and potentially a higher incidence of fractures than expected. In any case, it appears that patients with breast cancer are not protected from osteoporosis, which provides further support for the recommendation that bone health is assessed after a diagnosis of breast cancer. Most adjuvant therapies will lead to increased bone loss and a higher fracture rate. Among the adjuvant therapy options for premenopausal patients with breast cancer, endocrine therapy (ovarian suppression) and chemotherapy can result in cancer treatment-induced bone loss (CTIBL) of up to 10% at the lumbar spine after one year. Antiresorptive therapies prevent CTIBL in premenopausal women with breast cancer. Most of the evidence demonstrating the efficacy of bisphosphonates in the prevention of CTIBL is derived from clinical trials with zoledronic acid. The addition of zoledronic acid 4 mg per six months to adjuvant endocrine therapy maintained and even increased bone mass during a 3-year treatment period and significantly improved disease-free survival in a population of young women who underwent menopause due to the adjuvant treatment. The major contributor to bone loss in the adjuvant treatment of breast cancer in postmenopausal women is the use of aromatase inhibitors (AIs). Oncology trials have underestimated the fracture risk in the setting of AI-induced bone loss. In the ABCSG-18 study, the only trial in which fracture incidence was the primary endpoint, the rate of clinical fractures was close to 10% after 3 years in the placebo group on AIs only. Bisphosphonates and denosumab at osteoporosis treatment doses can counteract AI-induced bone loss. In the ABCSG-18 trial, treatment with denosumab 60 mg injection every 6 months reduced the risk of first clinical fracture relative to placebo by 50%. Current guidelines recommend antiresorptive therapy in patients with a baseline T score of < -2.0 or with two or more clinical risk factors for fracture. These recent guidelines will need to be updated, as similar significant protective effects were seen in women with either normal or low bone mass. Moreover, a formal meta-analysis of individual patient data from more than 18,000 women in 26 randomized trials of adjuvant zoledronic acid or clodronate treatment for early breast cancer revealed that bisphosphonates significantly reduced the risk of first distant recurrence in bone and the risk of breast cancer mortality, at least in postmenopausal women. Even though the increased risk of fracture during adjuvant treatment for breast cancer in postmenopausal women is notable, an enhanced risk of fracture in long-term survivors of breast cancer remains under debate. The most recent studies suggest that Caucasian breast cancer survivors do not have a significantly increased risk of osteoporotic fracture over the long term.

1. Introduction

Breast cancer is among the most common types of cancer in women. Compared to older endocrine therapies, an increase in the survival of patients with hormone receptor positive breast cancer has been observed with the introduction of adjuvant therapy such as tamoxifen and

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http://dx.doi.org/10.1016/j.maturitas.2017.08.008
Received 26 July 2017; Received in revised form 7 August 2017; Accepted 11 August 2017

aromatase inhibitors (AIs) [1–3]. A recent meta-analysis has shown that the risk ratios for recurrence favoured AIs during periods when the treatments differed (Relative Risk [RR] 0.70, 0.64–0.77), and all-cause mortality was also reduced with AIs (RR 0.88, 0.82–0.94; p = 0.0003) [4].

Less than 10% of women are diagnosed with metastatic disease at presentation; hence, the majority of breast cancer patients are treated with an intention to cure. With more women surviving breast cancer longer, maintaining their quality of life and avoiding treatment complications are of primary importance. However, because the bone is also an endocrine organ, these anti-hormonal therapies can have a negative impact on bone health. Indeed, both AIs and tamoxifen inhibit the stimulating effect of oestrogen on breast tissue [5,6]. Consequently, monitoring the long-term effects of anti-hormonal therapies, including bone health, is important.

The objective of this narrative review is to discuss the relation between breast cancer and bone health with a special focus on four issues of potential relevance to the clinician: the fracture rate in breast cancer patients before therapy, increased bone loss and fracture rate during adjuvant therapy of breast cancer in premenopausal women and in postmenopausal women and the fracture rate in long-term breast cancer survivors.

2. Methods

The Belgian Bone Club board invited 8 experts in musculoskeletal diseases and/or cancer (endocrinologists, rheumatologist, geriatrician, clinical epidemiologists and scientists) to be part of a working group discussing skeletal health in cancer survivors. Two of the participants were entrusted with the task of preparing a literature review. A literature search was conducted in May 2017 using the MEDLINE/PubMed database. The search strategy included a combination of the following terms: cancer, recovery, survival, bone, osteoporosis, osteopenia and fracture. Additional references were selected from the reference lists of the retrieved articles to broaden the literature search. Only articles published in English were considered. This literature search yielded more than 500 hits of which only a substantial subset was retrieved according to their relevance to the topic. Our literature review focused on the most robust available evidence when possible, such as meta-analyses and prospective studies, with the most recent publications consulted.

3. Results and discussion

3.1. Is the fracture rate decreased or increased in breast cancer patients before therapy?

Some surrogate markers of the lifetime exposure to oestrogen could be considered to play different roles in fractures or breast cancer [7,8]. Indeed, late menarche, early menopause and a low body mass index, are associated with an increased risk of osteoporotic fractures, whereas early menarche, late menopause, postmenopausal use of Hormonal Replacement Therapy (HRT) and high body mass index are known to be risk factors for breast cancer. Thus, identifying the risk factors that increase the incidence of breast cancer should theoretically help protect against fracture occurrence. Moreover, a meta-analysis without specific populations restriction, reported that a higher bone mineral density was associated with a significantly higher risk of breast cancer in postmenopausal women [9]. The meta-analysis suggested that individuals in the highest category of hip or spine BMD had a 62 or 82% higher risk of breast cancer compared with those in the lowest category. Consistent with this observation, prospective studies have suggested that patients with bone fractures were at lower risk of breast cancer [10,11].

No prospective studies are available to assess the relation between the incidence of fractures and breast cancer before therapy since most of the patients are treated after its diagnosis. Since most of the current − and past − treatments used in the management of breast cancer could have an impact on bone health, they could be considered as potential confounding factors when assessing the long-term relation between breast cancer and bone heath.

Moreover, very few cross-sectional studies are available assessing the prevalence of fractures in breast cancer patients before the initiation of specific therapies. In a Spanish study of 343 women with early breast cancer, aged 62 years on average, who were about to start adjuvant AI therapy, 17.7% had normal BMD, 60.1% had osteopenia, 22.2% had osteoporosis and 11.4% had a prevalent fracture [12]. In another French study of 497 women with a mean age of 64 years who were enrolled before starting AIs, 31.4% had a low bone mass (T-score < 2 SD), 19.7% had vertebral fractures and 19.1% had a history of non-vertebral fractures [13]. These percentages are higher than expected in a population of the same age and ethnicity without cancer, but caution must be taken when interpreting these results because both of these studies suffer from the lack of a control group without breast cancer.

In the various AI trials, even if the prevalence of fractures at baseline was not reported, a very low proportion of women with osteopenia or osteoporosis was noted [14–16]. This finding suggests that patients included in the large clinical trials might differ from those seen in actual practice. That could have some implications when generalizing the results of fracture incidence in these large clinical trials. Despite the limited amount of data, these results suggest that bone health status should be assessed after a diagnosis of breast cancer.

3.2. Increased bone loss during adjuvant therapy of breast cancer in premenopausal women

Bone loss results from age, lifestyle, disease and treatment-related influences on the normal bone turnover, more so at sites of the skeleton characterized by a higher proportion of trabecular bone (e.g., the spine and the proximal and distal ends of long bones). Bone loss leads to thinning and perforation of the trabecular plates, and the subsequent loss of normal architecture results in a disproportionate loss of strength for the amount of bone lost, especially when the bone loss is markedly accelerated. Oestrogen deficiency is the major cause of accelerated bone loss leading to an increased incidence of fractures. In the setting of adjuvant treatment for breast cancer, current treatment guidelines recommend that premenopausal women with hormone receptor-negative disease receive adjuvant chemotherapy, and those with hormone receptor-positive disease receive adjuvant endocrine therapy (tamoxifen ± ovarian function suppression) with or without adjuvant chemotherapy [17].

Among these adjuvant therapy options for premenopausal patients with breast cancer, both endocrine therapy (tamoxifen whether combined or not with ovarian suppression using GnRH agonists) and chemotherapy can result in substantial bone loss from the suppression of oestrogen levels, premature menopause, or direct negative effects of chemotherapy on bone [18–20]. Amenorrhea can therefore result from ovarian function suppression or chemotherapy-induced ovarian failure. Chemotherapy-induced ovarian dysfunction accelerates the onset of menopause by an average of 10 years [21]. Between 25% and 100% of premenopausal women may experience early menopause or amenorrhea, especially in women over 40 years of age [22]. Chemotherapy-induced ovarian failure results in substantial bone mineral density (BMD) loss of up to 6–8% at the lumbar spine after 1 year [23,24]. Ovarian function suppression with luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin leads to a mean 10.5% loss of BMD at the lumbar spine and 6.4% at the femoral neck [25]. Tamoxifen alone and in combination with a LHRH agonist are standards of care for women with oestrogen receptor-positive breast cancer. Although tamoxifen is a selective oestrogen receptor modulator with some bone protective activity in postmenopausal women, it has also been associated with bone loss in premenopausal patients [18]. Changes in BMD

or biochemical markers of bone resorption are surrogate markers for fracture risk due to cancer treatment-induced bone loss (CTIBL), but no fracture data are available in this particular adjuvant setting.

Antiresorptive therapies can effectively prevent CTIBL in premenopausal women with breast cancer. Most of the evidence for the efficacy of bisphosphonates in the prevention of CTIBL is derived from clinical trials of zoledronic acid [23]. Zoledronic acid 4 mg, probably preferably every 3 months as opposed to every 6 months over 1 year, can completely prevent bone loss due to chemotherapy-induced ovarian failure with a sustained benefit 1 year after completion of therapy [26]. On the other hand, the Austrian Breast and Colorectal Cancer Study Group 12 (ABCSG-12) trial has been the main preventive study of CTIBL induced by hormonal therapy in premenopausal women [27]. More than 1800 premenopausal women with early-stage breast cancer received primary adjuvant endocrine therapy (ovarian suppression plus tamoxifen or anastrazole) with or without zoledronic acid (4 mg every 6 months) for 3 years. The addition of zoledronic acid to adjuvant endocrine therapy maintained and even increased BMD during the 3-year treatment period compared with a significant BMD loss in the patients who did not receive zoledronic acid (-11.3% at the lumbar spine; -7.3% at the trochanter; $P < 0.0001$ for both) [27]. The benefit was sustained for at least 2 years after the end of the trial. Moreover, adding zoledronic acid to adjuvant endocrine therapy significantly improved disease-free survival, and there was a trend for improved overall survival. Subgroup analyses confirmed anticancer benefits only in women older than 40 years [27]. The tolerance of zoledronic acid at these therapeutic schedules is excellent [28]. The selection of patients for such prevention treatment remains, however, unclear.

Current fracture risk assessment tools are based on data from healthy postmenopausal women and do not adequately address the risks associated with treatments in younger premenopausal women. Moreover, the International Society for Clinical Densitometry recommends using Z-scores in premenopausal women, which represent the standard deviation of BMD relative to the expected BMD range for women of similar age. Guidance from expert groups for premenopausal women with breast cancer recommends that all premenopausal women be informed about the potential risk of bone loss before beginning anticancer therapy, with the use of antiresorptive therapy if the BMD Z-score is < -2 or if the score is ≤ -1.0 with an annual decrease of BMD of 5% to 10% [23]. We believe, however, that the clinicians should not wait until such degree of bone damage occurs, and we believe that antiresorptive therapy with zoledronic acid should be considered in all premenopausal women with a low bone mass, i.e., a Z-score less than -1, when starting hormone ablative therapy in premenopausal patients with breast cancer.

3.3. Increased bone loss and increased fracture rate during adjuvant therapy of breast cancer in postmenopausal women

The major contributor to bone loss in the adjuvant treatment of breast cancer in postmenopausal women is the use of aromatase inhibitors. AIs improve the disease outcomes compared to tamoxifen and have become the first-line hormonotherapy in the adjuvant setting of breast cancer, but bone loss is their main side effect. AI therapy is associated with an average 2% loss of BMD at the lumbar spine per year, and the effects of AIs on cortical bone and bone strength appear to be largely underestimated by classic dual-energy X-ray absorptiometry (DXA) [29]. The FRAX model does not include anti-cancer treatments as a specific risk factor and underestimates the fracture risk in the setting of AI-induced bone loss. These agents prevent the conversion of androgens to oestrogen by the aromatase enzyme, thereby rapidly and dramatically reducing circulating serum oestradiol levels. In oncology trials, this decline in oestradiol was associated with a 40% relative increase in fracture rate compared to tamoxifen. When compared to placebo, the excess fracture rate during AI therapy was considered to be less, but the risk has actually been underestimated because the fractures were only reported as adverse events in oncology trials [30]. The increased risk is independent of the type of AI and, in the ABCSG-18 study, the only trial in which the fracture incidence was the primary endpoint, the fracture rate was 9.6% after 3 years and 26% after 7 years in the placebo group receiving AIs only [31].

Pharmacological intervention for patients at risk of bone loss includes vitamin D supplementation (1000–2000 IU daily) and calcium supplementation (1000 mg daily) is recommended if the dietary intake is inadequate. Antiresorptive therapy is recommended in patients with a baseline T score of < -2.0 or two or more clinical risk factors for fracture [29]. Data from randomized clinical trials (RCTs) in > 5000 patients show that bisphosphonates and denosumab administered at doses and schedules that are most often similar to those used for postmenopausal osteoporosis can prevent bone loss in women with breast cancer and even lead to an increase in BMD [29,32]. In postmenopausal women, the choice of bisphosphonate is broader than in premenopausal women, with evidence that ibandronate (150 mg oral monthly), clodronate (1600 mg oral daily), risedronate (35 mg oral weekly), alendronate (70 mg oral weekly) and zoledronic acid (4 mg IV 6 monthly) all prevent the bone loss associated with the use of AIs [32]. Although these trials were not designed with a fracture-prevention endpoint, data from the osteoporosis setting have demonstrated a good correlation between BMD improvements and fracture prevention. The ABCSG-18 trial, which randomized postmenopausal women on AIs to denosumab 60 mg injection every 6 months or placebo, found that active treatment reduced the risk of first clinical fracture relative to placebo by 50%. Five years following randomization, 15% of placebo patients but slightly over 5% of denosumab-treated patients had experienced a fracture. A similar significant protective effect was seen both in women with a baseline T-score < -1 and in those with a T score ≥ -1. Since anti-resorptive treatments can cause osteonecrosis of the jaw, the investigators established a proactive screening and monitoring system within the trial. Despite this approach and expert adjudication of suspected episodes of dental problems, they did not identify any cases of osteonecrosis of the jaw. Furthermore, atypical fractures have been reported with anti-resorptive agents, but were not seen in ABCSG-18.These new findings will have to be considered when updating the guidelines for the prevention of AI-induced bone loss, especially given that denosumab was not associated with additional toxicity [31,33]. An increased risk of multiple vertebral fractures on denosumab discontinuation has recently been described in case reports, particularly in patients with prior vertebral fractures. Although no guidelines are yet available in the setting of CTIBL, when denosumab is stopped, we advise to start a replacement antiresorptive therapy to sustain antifracture efficacy.

Several other trials evaluating zoledronic acid primarily as a bone protective agent during AI treatment for postmenopausal women with breast cancer also investigated the effects of bisphosphonate use on disease outcome. The largest of these trials (ZO-FAST) reported fewer recurrences in women receiving immediate bone protection with zoledronic acid compared with the control arm where the bisphosphonate was only introduced months or years later if there were changes in BMD or a fracture that warranted intervention [34]. The improvement in disease outcomes in both zoledronic acid and oral clodronate trials were predominantly and most consistently mediated by a reduction in bone metastases as the first distant metastatic site. To investigate the available evidence in a more robust and precise fashion, the Early Breast Cancer Trials Collaborative Group (EBCTCG) has conducted a formal meta-analysis of individual patient data from 18,766 women in 26 randomized trials of adjuvant bisphosphonates for early breast cancer [35]. The majority of these patients received either oral clodronate 1600 mg daily or intravenous zoledronic acid 4 mg every 6 months. For the entire population, bisphosphonates reduced both the number of patients with first distant recurrence in bone (RR = 0.83; 95%CI 0.73–0.94, p = 0.004) and the incidence of breast cancer mortality (RR = 0.91; 95%CI 0.83–0.99, p = 0.04). The effect was larger

when the analysis was restricted to postmenopausal women (n = 11767). In these women, bisphosphonates improved not only recurrence in bone (RR = 0.72; 95%CI 0.60–0.86, p = 0.002) but also overall breast cancer recurrence (RR = 0.86; 95%CI 0.78–0.94, p = 0.002) and, most importantly, markedly reduced breast cancer mortality (RR = 0.82; 95%CI 0.73–0.93, p = 0.002). Bisphosphonates did not appear to modify any disease outcomes in premenopausal women [35]. From the data provided, the authors state they were unable to assess the incidence of osteonecrosis of the jaw, but previous reports suggest it ranges from under 1% with clodronate, ibandronate, or 6-monthly zoledronic to about 2% with more intensive zoledronic acid schedules for 3–5 years of therapy. The risk-benefit ratio is thus largely favourable even if the selection of patients for such prevention treatment remains, however, unclear. A European expert panel concluded that the data supported the use of adjuvant bisphosphonates in postmenopausal women, but experts were divided on restricting the adjuvant use of these antiresorptive agents to women considered at intermediate or high risk of recurrence rather than the unselected use across all risk groups. The panel was in agreement that either daily oral clodronate or intravenous zoledronic acid (every 6 months) are the preferred agents and recommended treatment for 3–5 years [36]. The results of trials testing the antitumor efficacy of denosumab in the adjuvant setting are eagerly awaited and should be available soon.

4. Fracture rate in long-term breast cancer survivors

Studies of bone health status among survivors of breast cancer published more than a decade ago have provided conflicting results but tended towards an increased risk of fracture [37–40]. For example, the Women's Health Initiative showed that postmenopausal survivors of breast cancer are at increased risk for clinical fractures [40] but the Long-term Survivorship in Older Women with Early-stage Breast Cancer (BOW II) study suggested that long-term survivors of early-stage breast cancer diagnosed at age 65 or older are not at increased risk of osteoporotic fractures compared to age-matched women without breast cancer [39]. However, these studies have some limitations such as not taking into account the prevalence of fracture, stage of the disease or treatment use. Moreover, these studies were designed before the use of AIs for hormone responsive breast cancer, a treatment that negatively affects bone health, as reported in the previous section.

More recent studies have attempted to overcome these limitations. In a population-based historical cohort study of 608 US women with invasive breast cancer followed for 5776 person-years, the standardized incidence ratio was 1.2 (95% confidence interval [CI] 0.99–1.3) for total fracture risk and 0.9 (95% CI 0.7–1.2) for osteoporotic fracture risk alone [41]. In another study, 1286 women aged 65 and older who were alive and recurrence-free 5 years after a diagnosis of early-stage breast cancer and the same number of matched controls were followed for 10 years [42]. At the end of the follow-up period, no difference was observed in the fracture rates between groups (hazard ratio (HR) = 1.1, 95% confidence interval (CI) = 0.9–1.3).

The site of fracture is also of interest. Indeed, trabecular bone sites such as the spine are metabolically more active than cortical bone sites and are likely to be a more sensitive indicator of abnormal bone metabolism. An interesting study was designed to look at the special and temporal fracture pattern in breast or gynaecological cancer [43]. Despite the limited number of subjects included (n = 139), the pattern of skeletal fracture was similar between cancer survivors and the general population. The most common fracture sites were the vertebrae (16%), feet and toes (15%), ribs (12%), hands and fingers (10%), and pelvis (8%). The authors also showed that the median time from cancer diagnosis to fracture varied according to age (p < 0.01), from a high of 3.2 years for ages 50–59 to a low of 1.2 years for patients older than 70 [43].

The consequences of fractures have also been compared between cancer survivors and control subjects. In a study performed in Sweden, it was shown that compared with the general population, breast cancer patients had incidence rate ratios of 1.25 (95% CI: 1.23–1.28) and 1.18 (95% CI: 1.14–1.22) for hospitalization due to any bone fracture and hip fracture, respectively [44]. However, it should be noted that the comorbidities at baseline, assessed with the Charlson index, were associated with the risk of being hospitalized with bone fracture.

At last, it should be noted that all these studies have been mainly performed on Caucasian women and that the association in other ethnic groups may yield different results. For example, in a study performed on 22,076 Taiwanese women with breast cancer, the incidence of all types of fracture was higher in the breast cancer cohort than in the 88,304 women without cancer, with adjusted HRs of 1.18 (95% CI, 1.03–1.35) for hip fractures, 1.12 (95% CI, 0.98–1.28) for forearm fractures and 1.24 (95% CI, 1.04–1.48) for vertebral fractures [45].

In summary, the relation between breast cancer survival and future risk of fracture remains under debate, although the most recent studies suggest that Caucasian survivors do not have a significantly increased risk of osteoporotic fracture. However, it should be noted that all these observational studies must be interpreted with caution because potential limitations such as the potential confounding by treatment indication are likely to be present and are very difficult to take into account.

Contributors

OB performed the initial literature research and wrote the first draft of the manuscript.

JJB performed the initial literature research and wrote the first draft of the manuscript.

All authors analysed and interpreted the data, and all authors revised the paper and saw and approved the final version.

Conflict of interest

All authors declare that they have no conflict of interest related to this paper.

Funding

No funding was received for this review.

Provenance and peer review

Peer review was directed by Professor Margaret Rees independently of Serge Rozenberg (one of the authors and an Editor of *Maturitas*), who was blinded to the process.

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