Published in final edited form as:

Maturitas. 2012 December ; 73(4): 275–279. doi:10.1016/j.maturitas.2012.08.009.

The Management of Osteoporosis in Breast Cancer Survivors

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Abstract

Breast cancer is a common diagnosis and the majority of women treated will be cured. Women with early stage breast cancer may be at increased risk for osteoporosis due to anticancer therapies. Chemotherapy induced amenorrhea and the use of anti-estrogens can promote bone loss; thus, the management of bone health in women with breast cancer is an important component of survivorship care. Osteoporosis is considered a “silent” disease as there are often no discrete warning signs, until a fracture occurs; therefore, clinicians must be cognizant of the underlying risk for osteoporosis and co-morbid conditions and/or medications that accelerate risk of fracture. Breast cancer therapies that effect bone, screening for bone loss and interventions to mitigate the treatment toxicities are reviewed.

Keywords

Breast Cancer; Bone Health; Osteoporosis

Introduction

Breast Cancer

In 2012, over 200,000 women in the United States are expected to be diagnosed with breast cancer, the most common type of cancer affecting women. The median age at breast cancer diagnosis is 61 years [1]. Less than 10% of women are diagnosed with metastatic disease at presentation; hence, the majority of breast cancer patients are treated for cure. With more than 2 million breast cancer survivors [2] in the USA, monitoring the long-term effects, including bone health, is important

Breast cancer therapies administered in the adjuvant setting are used with curative intent. Approximately 70% of breast cancers express the estrogen and/or progesterone receptor; hence anti-hormonal therapies are often used to reduce the risk of breast cancer recurrence [3]. As bone is an endocrine organ, these anti-hormonal therapies can have a negative

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impact on bone health. Chemotherapy regimens may also have a negative impact on bone health. The term Cancer-Treatment- Induced Bone Loss (CTIBL) is now a recognized entity among the medical community. This review will address the prevention and management of CTIBL in women with early stage (non-metastatic) breast cancer.

Low bone mass

Low bone mass is a major public health threat to women 50 years of age and older: approximately 45% of women over age 50 years have either osteopenia or osteoporosis as defined by the World Health Organization [4], both of which increase the risk of fracture [5]. Due to the demographics of the aging population, it is estimated that by 2020, over 60 million Americans in the US will be at risk for fractures [6]. Although osteoporosis is associated with an increased risk for fracture, most women who experience fractures have osteopenia, by virtue of the larger proportion of women in this category [5]. Approximately one in two women will sustain a fragility fracture in their lifetime [6]). Many fractures have a negative impact on quality of life and can be associated with chronic pain, disability and loss of independence, as well as death. Increased mortality is associated with hip fractures; 24% of hip fracture patients over age 50 die within a year of this often devastating fracture [6]. The overall annual incidence of osteoporotic fractures is greater than that of breast cancer, heart attack and stroke combined. Estimates suggest that osteoporosis will be responsible for approximately three million fractures worldwide at a cost of \$25.3 billion annually [6]. Thus, the problem of osteoporosis and fractures is not insignificant, and is an important one in women with breast cancer.

Methods

To identify reports of bone health in women with breast cancer a literature search was performed using PUBMED. Studies published in English with a preference for papers reported after 2000 were identified. Abstracts published after 2010 from the American Society of Bone and Mineral Research and the American Society of Clinical Oncology were also reviewed.

Bone Health and Breast Cancer

Data from the Women's Health Initiative Observational Study (WHI-OS) suggests that postmenopausal women with a history of breast cancer may be at an increased risk for clinical fractures [7]. In the WHI-OS analysis women with a history of breast cancer had 68.6 more fractures per 10,000 person years compared with women without breast cancer. Importantly, this analysis was done in women treated with tamoxifen, as the study was done before the use of aromatase inhibitors (AI) for hormone- responsive breast cancers. Recent data on AIs has demonstrated higher rates of fractures than tamoxifen [3].

The data addressing bone health in women with breast cancer is not uniform. As increases in BMD and increases in risk for breast cancer may be associated with greater exposures to estrogen, there is the possibility that women with breast cancer have a higher BMD at baseline. Of note, there is data that women with a history of breast cancer may have a decreased risk of hip fractures [8]. The field continues to investigate this issue.

Chemotherapy

Preclinical studies have demonstrated that cyclophosphamide, doxorubicin and methotrexate may have a negative impact on bone cells [9]. These chemotherapies are commonly used in the management of breast cancer, and may promote ovarian dysfunction and accelerate bone loss in premenopausal women. The risk of premature menopause is influenced by the

chemotherapy drugs used and the woman's age at time of therapy. Approximately 70% of premenopausal women will experience chemotherapy related amenorrhea and/or premature menopause [10]. Concerns exist for premature menopause increasing the risk for developing osteoporosis and fractures.

The chemotherapy insult to bone may not be limited to premenopausal women. A study of postmenopausal women with early stage breast cancer identified a lower bone mineral density (BMD) in those who had received chemotherapy versus those who did not [11], and a small prospective study of postmenopausal women with breast cancer demonstrated rates of bone loss ranging up to 10% in one year [12]. Larger studies of BMD in postmenopausal women receiving chemotherapy are ongoing (NCT00603551) and results are eagerly awaited [13].

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, has both agonist and antagonist effects. In premenopausal women with hormone receptor positive breast cancer tamoxifen is the standard adjuvant endocrine therapy. In postmenopausal women tamoxifen may be used alone, or in sequence with an AI [3].

Tamoxifen exerts an estrogen agonist effect in bone that may counteract postmenopausal bone loss. Studies in the 1990's showed the beneficial effects of tamoxifen on bone in postmenopausal women where BMD increased at the lumbar spine and hip by approximately 0.5-1.0% per year while it decreased in the placebo group [14-18]. In premenopausal women, tamoxifen can have a negative effect on bone and trials have shown decreased BMD in this population [14,19]. In young women who have experienced chemotherapy induced amenorrhea, the effect of adjuvant tamoxifen on bone is influenced by menopausal status [19]

Aromatase Inhibitor

Aromatase is the key enzyme involved in the peripheral conversion of androgens to estrogen, and in the adrenal gland, androstendione to estrone. The AIs, block the activity of this enzyme and are potent anti-estrogens. Adjuvant AI's have been shown to increase disease free survival above that seen with tamoxifen in postmenopausal women with hormone receptor positive breast cancer [3]. AIs are used alone or sequentially following tamoxifen. The typical duration of adjuvant endocrine therapy is a total of 5 years, although 5 years of tamoxifen may be followed by 5 years of aromatase inhibitors. The AIs are excellent therapies for breast cancer; however, both the steroidal (exemastane) and the non-steroidal AI's (letrozole and anastrozole) have been associated with bone loss and fractures [20-22].

In the Phase III clinical trial of anastrozole, tamoxifen, alone or in combination (ATAC) the bone sub-protocol examined 308 women. Of the 81 women in the anastrozole group there was a 7.24% decline in BMD at the total hip and -6.08% at the lumbar spine. Fracture rates were higher in the anastrozole group, but none of the women developed osteoporosis if they had a normal BMD at baseline [23]. This decline in BMD was not completely reversible but an increase in BMD was seen 1 and 2 years after completion of therapy. In the Breast International group 1-98, patients on letrozole had significantly higher rates of fractures compared with tamoxifen [21]. Lonning et al compared the steroidal AI, exemastane with placebo and saw a significant decrease in femoral neck BMD after 2 years of therapy with a partial recovery once the drug was discontinued demonstrating that the steroidal AI also has a negative clinical impact on bone [24]. Regardless of the AI and whether it was used

upfront, sequentially or as extended treatment, they are associated with increased bone turnover, decreased BMD and increased fracture rates [3].

Management Issues

Bone Mineral Density (BMD)

The risk of fracture is influenced by BMD and bone quality. Both American Society of Clinical Oncology (ASCO) [25] and the National Comprehensive Cancer Network (NCCN) [26] have proposed guidelines for the management of bone health in the breast cancer population that includes monitoring BMD, as well as counseling patients on weight bearing exercise and adequate intake of calcium and vitamin D. The ASCO and NCCN guidelines are generally in line with those of the US Preventive Task Force (USPTF) which recommends BMD screening in women ≥ 65 years, treatment with aromatase inhibitors, or younger women with risk factors including premature ovarian failure [25-27].

Fracture Risk Assessment Tool (FRAX)

The online program FRAX is a tool developed by the World Health Organization (WHO) and the National Osteoporosis Foundation to estimate 10-year risks for fractures (www.shef.ac.uk/FRAX) [28]. The tool, used for patients with osteopenia, assesses a number of clinical risk factors including age, height, body mass index, subject and parental fracture history, secondary osteoporosis, glucocorticoids, tobacco and alcohol which are weighted according to their significance in the analysis. FRAX can also be used if BMD is not available. Importantly it does not include medication use such as tamoxifen, AIs, duration or dosing of glucocorticoids, vertebral fractures or bone turnover markers.

Some suggest that FRAX will underestimate the risk of fractures in women on AIs because the “secondary osteoporosis” risk factor does not carry sufficient weight in the overall analysis [29]. In a single-center, retrospective, database analysis Hadji et. al, evaluated over 1000 pre and postmenopausal women with receptor positive breast cancer to determine recommendations for anti-resorptive therapy using 5 different suggested guidelines including FRAX, ASCO, WHO, expert consensus by the primary author and German Dachverband Osteologie [30]. These investigators found that the recommendation for anti-resorptive treatment was consistent in only 4-5% of cases and recommendation against treatment was higher at 57%. This left 30-40% of patients with inconsistent recommendations regarding therapy. This data points to the need for further studies to determine those who would benefit from anti-resorptive therapy.

Co-morbid conditions that promote osteoporosis and fracture may be present in women with breast cancer and should be considered during assessment and treatment planning. Common diagnoses include vitamin D insufficiency or deficiency and idiopathic hypercalciuria as well as primary hyperparathyroidism [31, 32]. These risk factors are not part of the FRAX analysis.

Calcium, Vitamin D and exercise

The calcium and vitamin D intake recommendations by ASCO are in line with the USPTF and include approximately 1200 mg/day of calcium and 600-800 IU/day of vitamin D, ideally through dietary intake [25, 27]. Although the USPTF has recently recommended against taking calcium and vitamin D to prevent fractures based on the available evidence, these recommendations are for the general public and do not necessarily apply to women with breast cancer. In our own clinics we recommend 1200 mg of calcium per day (dietary is preferred source) and 800 – 1000 IU/day of vitamin D in this population. Serum levels of 25-OH vitamin D, a reflection of nutritional stores can also be measured, and our preference

is to maintain a level between 30-35 ng/ml, in women on AIs. However, ideal levels in this population have not been established, and trials studying the management of bone health including vitamin D supplementation are ongoing (VITACAL: NCT01480869).

Exercise

There are limited data regarding exercise to prevent CTIBL in breast cancer survivors. Moderate intensity aerobic exercise or resistance training with exercise bands or usual care was evaluated in women receiving chemotherapy [33]. Aerobic activity was able to maintain BMD at the spine compared with usual care where significant loss was seen. Resistance training did not offer sufficient benefit possibly because ability to achieve adequate exercise intensity was a factor. In another study in women receiving chemotherapy, daily walking programs compared with bisphosphonates did not prevent spine bone loss; however, participants had a high level of activity at baseline and insufficient bone loading may have been a factor [34].

Other trials have focused on the benefits of aerobic or resistance training after treatment for breast cancer and have found mixed results [35]. One study reported preservation of spine BMD after 12 months of moderate to vigorous resistance training compared with a stretching-only control group [35]. In another study of 249 women, the addition of resistance training to an oral bisphosphonate improved hip and spine BMD above bisphosphonate alone, but gains were not significant [36].

The current recommendations for exercise in women on cancer therapies are consistent with general population recommendations. Moderate to high intensity exercise seems to improve spine BMD; however, improvement of hip BMD has not been demonstrated. Further study to improve or prevent hip BMD and to prevent falls is certainly warranted in this population of women, as hip fracture risk is increased [7].

Medical Therapies to improve BMD and fracture risk

Treatment Thresholds

Thresholds to initiate a medical therapy to prevent or treat osteoporosis are influenced by the risk of fracture. In general, the ASCO and NCCN guidelines are consistent with those of the National Osteoporosis Foundation (NOF) recommendations. However, the NOF have been updated to include FRAX and indicate that consideration be given to intervening with a FDA approved medical therapy when there is a history of a hip or vertebral fracture, a BMD of the femoral neck or spine within the osteoporotic range (T score ≤ -2.5) or FRAX results suggesting a 3% 10 year probability of a hip fracture or a 20% 10 year probability of a major osteoporotic related fracture [6]. In addition, clinical judgment and patient preference influence treatment decisions.

A consensus paper addressing CTIBL interventions for premenopausal women suggests that all women receive counseling on exercise, calcium and vitamin D intake, and that those who experience therapy-induced amenorrhea be considered for DXA imaging. This paper goes on to suggest that women with Z-scores < -2.0 or Z-score ≤ -1.0 and/or a 5–10% annual decrease in bone mineral density should be considered for bisphosphonate therapy [37]. The data on long-term effects of CTIBL is limited; hence, the guidance is extrapolated from other populations, which may also have limited long term data.

Treatment Options

In general, exogenous hormones (estrogen or parathyroid hormone) are not favored bone therapies in women with a history of breast cancer due to the concerns that these agents may

associate with an increased risk of cancer recurrence or new cancer [38]. The bisphosphonates are probably the most commonly used pharmacologic intervention to manage bone health in women with breast cancer.

In postmenopausal women receiving adjuvant aromatase inhibition, standard dosing of the oral bisphosphonates, demonstrated the ability to preserve, or increase BMD at 2 years [39-41]. Investigations of the intravenous bisphosphonate, zoledronic acid, and its ability to preserve BMD during adjuvant breast cancer care have used doses and intervals that are not FDA approved. In the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) changes in BMD were examined. Patients were randomized to receive zoledronic acid 4mg every 6 months upfront or added at the point when the T-score became -2.0 or lower. At 61 months Z-FAST demonstrated that upfront zoledronic acid treated patients had a greater rate of preserved or elevated BMD than that of the delayed group. The results of the Z-FAST study, examining zoledronic acid 4 mg every 6 months in women with osteopenia or normal BMD on adjuvant AI needs to be considered in light of the results published by Grey et al demonstrating that a single dose of zoledronic acid 5 mg suppressed bone turnover and showed an increase in lumbar spine and hip BMD at 5 years in postmenopausal women [42]. Whether similar long-term BMD results may be seen in women on AIs is not yet known.

BMD is a surrogate marker for fracture. In the meta-analysis of 14 adjuvant bisphosphonate clinical trials, Valachis et al found no evidence that adjuvant bisphosphonates reduced fracture rates in women with early stage breast cancer and the authors recommended against the routine use of bisphosphonate [43]. One of the major limitations of this study is that the eligible trials incorporated in the meta-analysis were not designed or powered to detect fracture. Ito and colleagues in their recent paper studied the cost effectiveness of fracture prevention for early breast cancer [44]. Annual BMD screening and treatment with bisphosphonates was found to be the most cost effective methods. The bisphosphonates, both oral and intravenous, have been studied for their ability to reduce the risk of bone loss associated with chemotherapy induced ovarian dysfunction, and as a whole the results show that the bisphosphonates mitigate bone loss in this setting [45].

Denosumab, a monoclonal antibody which targets the receptor activator of nuclear factor kappa-B ligand (RANKL), is FDA approved for the treatment of postmenopausal women at high risk for fracture as well as to increase bone mass in women at high risk for fracture receiving adjuvant AI therapy for breast cancer. The randomized clinical trial of denosumab 60 mg subcutaneously every 6 months in postmenopausal women with osteopenia receiving adjuvant aromatase inhibition was not designed with fractures as an endpoint [46]. This study demonstrated that denosumab increased lumbar spine BMD by 5.5% and 7.6% at 12 and 24 months respectively.

There is evolving data, and great enthusiasm, for the potential for osteoclast inhibitors to impact the risk of breast cancer recurrence. To date the data is mixed and the studies are reviewed elsewhere [47]. Additional clinical trials investigating osteoclast inhibition as an anticancer therapy are ongoing [48, 49]. Presently, it is standard of care to use the osteoclast inhibitors only as FDA labeled, unless as part of a clinical trial.

Summary

The majority of women diagnosed with breast cancer are treated for cure. With the expectation of long term survivorship, physicians should be aware of the potential for breast cancer therapy to impact bone health. The skeletal toxicities of breast cancer therapies are primarily through its effect on the endocrine system. Regardless of age or diagnosis of cancer, the foundation of bone health starts with adequate calcium and vitamin D intake, weight bearing exercise, and healthy lifestyles (no tobacco and limited alcohol

consumption). In addition to maintaining bone health, reducing the risk of falls can also reduce the risk of fracture.

Guidelines addressing bone health in women with breast cancer have been generated [25, 26, 29, 50] and in general, are consistent with recommendations for managing bone health in postmenopausal women and those with secondary osteoporosis. Additional breast cancer specific bone health data is needed to define the optimal management of bone health specific to women with breast cancer.

Acknowledgments

Catherine Van Poznak is supported by the NIDCR grant 5K23DE020197-04; Genetic Risk of Osteonecrosis of the Jaw (ONJ) in Patients with Metastatic Cancer

Funding: The NIH grant listed above is the only source of funding associated with this manuscript.

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