

Management options of breast cancer related osteoporosis

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Summary

Breast cancer therapy after surgery has been improved in recent years. Adjuvant therapies like aromatase inhibitors are being extensively used among breast cancer survivors. This led to cancer related and iatrogenic osteoporosis. Management of these patients needs to be focused and differentiated from the standard age related osteoporosis in women. All guidelines consider mandatory to assess fracture risk periodically in all breast cancer survivors. Risk assessment diagnostic FRAX tool is the most used but it's not born specifically for cancer related osteoporosis. The therapeutic management of this kind of osteoporosis has been studied by different societies. Since breast cancer survivors are at risk of osteopenia and osteoporosis, counseling regarding modifiable risk factors is mandatory and advocated. The beginning of the treatment should be tailored in each patient.

KEY WORDS: breast cancer; osteoporosis; women's health; bone resorption; drug therapy.

Introduction

Breast cancer is the most common cancer in women. Improvement in breast cancer treatment has been achieved in recent years. Therefore the majority of women with breast cancer are treated in early stages with higher free disease survival rate.

Surgical therapy tends to be more conservative as possible. Therefore, adjuvant therapy (radio and hormonal/chemotherapy) is playing a significant role in breast cancer treatment.

Since 70% of breast cancer express hormonal receptor (estrogen and progesterone), hormonal therapy in these women represents a milestone of the treatment.

There are many agents for adjuvant hormonal therapy, the most recent ones are aromatase inhibitors (AIs).

AIs has been demonstrated to be equal or superior to tamoxifen in treatment of postmenopausal women with breast cancer. Tamoxifen is associated with an increase in endometrial pathology and cancer and with greater odds of venous thromboembolism, whereas AIs are associated with greater odds of developing cardiovascular disease and bone fractures (1). In particular, AIs are associated with a reduction in bone mineral density (BMD) and an increase in fractures (2) whereas tamoxifen preserves BMD in postmenopausal women (3).

In post-menopause the main source of estrogens is the aromatase enzyme (4). AIs block aromatase enzyme that convert androgens into estrogens. The lack of estrogens cause bone remodeling and improve the activity of osteoclasts.

Osteoporotic fractures are one of the major causes of morbidity and mortality in postmenopausal women. Almost one third of hip fracture patients over age 50 die within a year (5).

Several guidelines has been created by the major scientific societies for management of breast cancer therapy induced osteoporosis.

For these reasons, nowadays monitoring side effects of breast cancer therapy is mandatory. The new challenge is the management of the long term effects of the therapy.

The American Society of Clinical Oncology (ASCO) (6), the Belgian Bone Club (7), the UK Expert Group (8), the National Comprehensive Cancer Network (NCCN) (9) and the European Society for Clinical and Economical aspects of Osteoporosis and Osteoarthritis (ESCEO) (10) proposed guidelines of prevention and treatment of osteoporosis in breast cancer survivors.

Several tools has been created for assessing bone health: FRAX is the most adopted one (11), and it was developed by the World Health Organization and the National Osteoporosis Foundation. It is an only software and it estimates ten year risks for fracture. FRAX assesses many risk factors such as age, weight, BMI, personal history of fracture, parental history of fracture, secondary osteoporosis, therapy with glucocorticoids, tobacco and alcohol use. Those factors are weighted in accordance to their impact on BMD.

FRAX does not include adjuvant therapy of breast cancer, thus the risk of bone fracture can be underestimated.

FRAX scoring guides the clinicians in the intervention for reducing bone fracture risk.

Other algorithms to calculate bone fracture risk have been developed by the National Osteoporosis Guideline Group (NOGG) (12), the National Osteoporosis Foundation (5), the German Dutch Verband Osteology (DVO) (13), and ASCO (6).

The role of biochemical markers of bone turnover should be further investigated to assess their ability to predict and possibly monitor bone loss in this setting.

Common treatment weapons for osteoporosis cancer-induced are calcium supplementation, vitamin D supplementation, bisphosphonates and denosumab.

The amino-bisphosphonates are first-line therapy for the treatment of most patients with osteoporosis, with proven efficacy to reduce fracture risk at the spine, hip, and other non-vertebral skeletal sites. Further, bisphosphonates have been associated with a significant decrease in morbidity and increase in survival (14, 15). The improved overall survival due to treatment with bisphosphonates has been reported in breast cancer survival too. It has been assessed that this therapy can be considered in an adjuvant clinical setting (16).

We performed a structured literature review to evaluate the best clinical management of osteoporosis in breast cancer survival using AI as adjuvant therapy.

Methods

We identified relevant English-language articles pertaining to management of osteoporosis risk of breast cancer survival by searching PubMed and EMBASE databases and searching on Google Scholar. The following search terms were used to identify primary articles: *breast cancer, AIs, osteoporosis, bisphosphonate and adjuvant therapy, fracture*. We then manually searched references from the primary articles. Only peer-reviewed reports were included and we excluded unpublished data.

Study selection and data analysis

Articles studying incidence and prevalence of bone loss due to breast cancer treatment were identified. Studies were eligible if they were RCTs and study participants received adjuvant treatment with an AI or international guidelines. If studies have multiple treatment arms, the AI- single-therapy groups were included.

Two authors independently extracted and checked data from articles.

Available recommendation for management of osteoporosis in breast cancer survivals

American Society of Clinical Oncology (ASCO) 2003 (6)

For breast cancer patients who have evidence of bone destruction on plain radiographs, intravenous pamidronate or zoledronic acid every 3 to 4 weeks are recommended.

Intravenous pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases, to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy because it was associated with a modest pain control benefit in controlled trials.

Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extra-skeletal metastases is not recommended.

Its use as adjuvant therapy is not recommended.

The management flow chart indicates screening by DXA only in high risk patients and starting of bisphosphonate therapy only in those with BMD under 2.5, as in non cancer patients.

Belgian Bone Club (7)

In 2007 the Belgian Bone Club indicated that bisphosphonate therapy should start early prior to occurrence severe osteoporosis to prevent or slow the rate of bone loss in patient receiving cancer treatment.

They consider for the treatment women with T-score less than -2.5 or history of fragility fractures and women with T-score between -1.0 and -2.5 plus other risk factors other than AIs therapy.

Risk factors are: older age, a prior history of fracture, a family history of hip fracture, previous and/or current use of systemic corticosteroids, a low body mass index, premature menopause, current smoking, high intake of alcohol.

UK Expert Group (8)

In 2008 the UK Expert Group modified the ASCO guidelines. In postmenopausal women they recommend intervention when T-score falls below -2.0 or if the rate of bone loss in women with pre-existing osteopenia exceeds 4% per year. In women receiving ovarian suppression plus an AI the recommended T-score threshold for intervention is -1.0, due to the very rapid losses of bone with occurs in this group of women averaging 16% over 3 years.

They also made an accurate flow chart writing 2 algorithms: one for women who experience premature menopause due to chemotherapy or ovarian suppression, ablation or removal and one for postmenopausal women receiving treatment with aromatase inhibitors.

The National Comprehensive Cancer Network (NCCN) (9)

In 2011 the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer and Prostate Cancer recommended that patients for whom planned therapy includes medications that lower sex steroids should be evaluated at baseline and with periodic follow-up DXA scans to evaluate risk of fracture.

Obtaining bone-related history and using the FRAX calculator to assess overall fracture risk are recommended to estimate fracture risk. Cancer patients at high risk should be evaluated every 12/24 months. NCCN report the current MEDICARE guidelines that recommend therapeutically intervention for patients with ten years FRAX risk of 3% for hip fractures and more than 20% for all major fractures.

To all patients it's mandatory to give a good counseling regarding modifiable risk factors as smoking, physical activity, alcohol use and also increase calcium and vitamin D intake.

Therapeutic intervention by i.v. or oral medication should be strongly considered in patients with a BMD below a T-score of -2.0.

In summary for NCCN it's very important the use of FRAX as risk assessment tool and DXA, starting therapy with a BMD under -2.0.

The NCCN Clinical Practice Guideline is not the most recent guideline, but we believe it's very interesting. It uses WHO recommendation, assessing the fracture risk using only FRAX tool plus BMD under -2.0, without considering all others risk factor singularly.

It is simply understandable by all physician in all over the world.

European Society for Clinical and Economical aspects of Osteoporosis and Osteoarthritis (ESCEO) (10)

ESCEO in 2012 analyzed all the previous available guidelines and propose a simpler flow algorithm.

All women starting a therapy with AIs should be carefully as-

essed for their baseline risk of osteoporotic fractures by performing a DXA, by a full evaluation of all clinical risk factors and using FRAX tool. A biochemical survey should include determination of calcium, PTH and vitamin D levels.

Premenopausal women with ovarian suppression undergoing tamoxifen or AI therapy should receive antiresorptive therapy if their T-score is below -1.0 or in case of vertebral fracture.

They recommend that antiresorptive treatment should be started in all osteoporotic women and, irrespective of BMD, in all women older than 75 years, and in patients with a prevalent fragility fracture.

Postmenopausal women with T-score less than 1.5 presenting at least one clinical risk factor should be treated, as well as those with a T-score between -1 and -1.5 presenting at least two clinical risk factors.

Alternatively, therapy could be considered in patients with a FRAX determined 10 year hip fracture probability $\geq 3\%$, which corresponds to the interventions threshold suggested in many countries, or a probability for major osteoporotic fractures of 20%.

Therapies to prevent bone mass loss

Strategies aimed at improving bone health in cancer patients include pharmacological and non-pharmacological options: lifestyle modifications, calcium and vitamin D supplementations. The usage of pharmacologic therapies with bisphosphonates and now Denosumab has become integral components of improving bone health in breast cancer survival. No published guidelines are available on duration of antiresorptive therapy and whether to institute drug holidays. BMD, response to therapy, and risk factors for continued bone loss or fracture must be considered for duration of anti-osteoporosis therapy.

Lifestyle modifications

Concerning lifestyle modifications it has been proven that moderate levels of activity such as walking and quitting both smoking and alcohol consumption have been associated with a decreased risk of hip fracture (17, 18).

Muscle mass, balance, and bone strength can be gained with physical activity. At least 30 minutes of moderate physical activity daily are recommended. Fracture risk reduction should also include strategies to prevent falls, such as checking for and correcting vision and hearing problems, evaluating for neurologic problems, reviewing prescription medications for side effects that may affect balance, and improving at-home safety.

A useful patient guide for bone health and lifestyle behavior is the NOF web site (19).

Calcium and Vitamin D supplementations

Current expert consensus guidelines recommend 1200 mg of elemental calcium supplementation with 800 to 1000 IU of vitamin D daily (20).

Bisphosphonates

Bisphosphonates reduce the risk of vertebral fracture by 30-70% in people with osteoporosis (21). Intravenous and oral bisphosphonates prevent AI-associated bone loss, but there are no studies on reduction of fracture in these patients (22). Bisphosphonates can reduce but do not completely abolish bone mass loss in patients with breast cancer and bone metastases in advanced breast cancer. On the other hand,

there are several studies that report the efficacy of zoledronic acid in preventing cancer-treatment induced bone loss (23-25). Given the role of bisphosphonates in treatment of osteoporosis, it has been reported their adjuvant function in breast cancer resulting in an increase survival rate. However, in literature the efficacy of bisphosphonates in the adjuvant clinical setting is still undefined. There are some studies where it has been demonstrated a positive action of this class of drug. Otherwise no benefit or disadvantages have been reported for adjuvant treatment of breast cancer with bisphosphonates. This lack of evidence should be due to many bias of the studies available in literature. The use of different bisphosphonates can impact on study result. For instance, oral administration has a lower bioavailability compared to IV administration, with different impact on breast cancer therapy. Therefore further studies are advocated to assess the real potential role of bisphosphonates in breast cancer therapy.

Denosumab

Denosumab is a fully human monoclonal antibody given subcutaneously that neutralizes the receptor activator of nuclear factor κ B ligand (RANK-L). RANK is an essential cytokine expressed on the surface of preosteoblastic and osteoblastic cells. RANK-L activates its receptor RANK, which is expressed on osteoclasts and their precursors, ultimately promoting osteoclast formation and activation. Therefore denosumab blocks osteoclast differentiation, proliferation, and function. The pharmacokinetics of denosumab has some advantages. It does not accumulate in bone, it has a circulatory half-life of approximately 26 days, and like other monoclonal antibodies, the clearance of denosumab is through the reticuloendothelial system and does not depend on renal clearance (26). In 2010 the FDA approved the use of denosumab in patients with bone metastases for preventing skeletal-related events.

Conclusions

A guideline that reflects accurately the need of antiresorptive therapy is still advocated.

We must consider that FRAX is not designed to assess fracture risk in breast cancer survivors and may underestimate the effects of AI therapy on bone.

ASCO guidelines are too old and can not take indications from the last 10 years of clinical trials with newer drugs.

ESCEO and NCCN are the most broad available guidelines. They evaluated BMD assessment by DXA and FRAX algorithms. On the strength of the current evidence, bisphosphonates are recommended for preventing bone mass loss in women receiving breast cancer therapy.

In the scientific community, the agreement for the threshold of T-score for the beginning of the treatment is low.

All guidelines consider mandatory to assess fracture risk and bone health in all breast cancer survival. Based on the fracture risk women should be start evaluation on bone loss periodically. If the fracture risk is elevated patients should be monitored every 12-24 months.

Since breast cancer survival are at risk of osteopenia and osteoporosis, counseling regarding modifiable risk factors is mandatory and advocated.

The beginning of the treatment should be tailored in each patient.

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