Translational Oncology & Therapeutics

Review Article

Adjuvant Therapy In Breast Cancer And Bone Health

Víctor Manuel Vargas-Hernández[1,2], Víctor Manuel Vargas Aguilar[3]

[1]*Academia Mexicana de Cirugia, Ciudad de México, CDMX, Mexico*

[2]*Academia Nacional de Medicina de Mèxico, Del. Cuauhtémoc, CDMX, Mexico*

[3]*Hospital Regional de alta especialidad de Ixtapaluca, Ixtapaluca, Méx., Mexico*

*Correspondence

Víctor Manuel Vargas Hernández

Women's Health Clinic, Insurgentes Sur 605-1403, Nápoles 03810, Ciudad de México

Tel: 55746647

E-mail: vvargashernandez@yahoo.com.mx

• Publication Date: 01 Oct 2022

Keywords

Breast cancer, menopause, survivors, Endocrine therapy, Bisphosphonates, Tamoxifen, Denosumab, Bone mineral density, Fracture risk. DXA.

Abstract

Background: breast cancer is the most common tumor in women worldwide and osteoporosis is linked to it, 70-80% of patients receive adjuvant endocrine therapy to improve prognosis; but, they accelerate bone loss and increase the risk of fractures by causing inflammation that stimulates bone breakdown and slows bone growth; Assessment of initial risk of fracture, monitoring of bone health and individualization based on initial risk, implementation of non-pharmacological measures, consideration of bone mineral density T-scores, guidance on criteria for starting antiresorptive treatment, choice of agents and duration of treatment, taking into account the oncological benefits of antiresorptive treatment. **Objective:** to analyze and evaluate the causes of bone loss in patients with breast cancer, adequate detection to estimate the risk of osteoporosis and fractures, prevention and therapeutic strategies for these, and the role of antiresorptive agents as adjuvant therapy. **Conclusions:** Despite advances in the management of bone loss induced by breast cancer, the optimal time to start antiresorptive agents and the duration of treatment remain unanswered; although, the evidence supports the use of therapeutic agents to protect bone health in breast cancer. Future clinical trials, as well as increased awareness of bone health, are needed to improve prevention, evaluation, and treatment in long-term breast cancer survivors.

Background

Breast cancer (BC), which is the most common tumor in women worldwide, regardless of age, is characterized by a peak incidence in postmenopausal age (50-69 years) [1]. The most common cause of bone loss in women is menopause and aging; this is associated with increased bone resorption and less bone formation, while menopause induces accelerated bone loss due to reduced estrogen levels. BC and its oncological management have a negative effect on bone health; leading to accelerated bone loss; It is considered the most common long-term adverse event, the decrease in bone mineral density (BMD) is mainly related to two factors, the onset of hypogonadism due to chemotherapy or endocrine therapies, added to bone loss related to menopause, are responsible for the appearance of osteopenia or osteoporosis (Op) and, as a consequence, fragility fractures. BC is a common condition that is often cured and the effects on bone health are important in survivors, as they are at risk of fractures that affect quality of life; the incidence of osteopenia, is an early indicator of bone loss, and Op in BC [2-4] survivors.

Osteopenia and osteoporosis, systemic skeletal conditions associated with varying degrees of bone loss, are prevalent in postmenopausal BC survivors, up to 80% have loss in BMD, leading to morbidity due to pain, fractures and death. Osteopenia is diagnosed with lower than average BMD, while Op is characterized by both low BMD and architectural deterioration of bone tissue. Among BC survivors, BC-related risk factors (RFs) for osteopenia and Op include both treatment and premature menopause. Importantly, the excess risk of osteopenia and Op in BC survivors, particularly those of a younger age, relative to women without BC remains unknown. Osteopenia and Op are prevalent in the general population. In women ≥ 50 years old, 15.4% have Op and 51.4% have low BMD in the EE.UU. it is estimated that 1 in 2 women will be at risk of suffering an Op-related fracture during their lifetime. In women without BC, bone density loss is associated with advanced age, menopause-induced estrogen deficiency, low body weight, sedentary lifestyle, excessive alcohol consumption, hereditary family history (AHF) of bone fracture, smoking, low calcium intake and vitamin D deficiency. BMD loss in BC survivors is due to similar RFs, in addition to effects related to cancer management, when compared to women without BC [5-8].

Impact of breast cancer and its treatment on bone health

Bone health is important for overall health and wellness, and even more so for BC patients and survivors. BC survivors had a 68% higher risk of Op and osteopenia compared to women without BC [9]. There is a very strong link between BC and

Citation: Vargas-Hernández VM, Vargas-Aguilar VM. Adjuvant Therapy In Breast Cancer And Bone Health. Transl Oncol Ther. 2022; 1(1):1-4.

its treatment, with involvement of the bone system and fracture risk. First of all, women with BC are usually postmenopausal with low BMD, even before starting oncological management, the vast majority begin treatment for BC often in the menopausal transition (MT), with major hormonal changes that are associated with accelerated bone loss and an increased risk of fractures during treatment, as well as throughout your life; in both premenopausal and postmenopausal women. In the Women's Health Initiative (WHI) study, BC survivors had a 15% higher risk of fractures compared to women without BC 10. Oncological management in the treatment of BC accelerate bone loss and includes chemotherapy, hormone therapy (Ht) due to hormonal blockage or ablation resulting in hypoestrogenism, antiestrogen therapy, radiotherapy (Rt) and concomitant medications such as corticosteroid therapy; they put patients at risk of Op and fragility fractures that compromise their quality of life and longevity [11-12].

Chemotherapy for CM has been associated with lower BMD in premenopausal and postmenopausal women [2,3–5]. In premenopausal women, Qt is often associated with ovarian dysfunction due to direct toxicity and interference with follicle maturation, leading to iatrogenic menopause and occurs about 10 years earlier than it would naturally; 40 to 95% of women undergoing chemotherapy develop premature ovarian failure, depending on the regimen and their age [5,6].

Premature menopause due to ovarian suppression with gonadotropin-releasing hormone (a-GnRH) agonists, bilateral salpingo-oophorectomy (SOB), or cytotoxic chemotherapy decreases circulating estrogen, which accelerates bone resorption and decreases BMD. α-GnRHs act on gonadotropin receptors in the pituitary gland, reducing estrogen production. The decrease in BMD is in the range of 3-7% in women receiving chemotherapy, 5% with a-GnRH increases 18-19% during 2 years after SOB. Short-term fractures are generally low in premenopausal women; these are treated with curative intent and are expected to have decades of life expectancy after completing BC therapy, thus making this significant early bone loss disadvantageous in their lives [5,6,11-12]. Antiestrogenic Ht with tamoxifen (TMX) and aromatase inhibitors (AI) has been the mainstay of treatment in BC with positive hormone receptors. TMX, a selective estrogen receptor modulator, has agonist and antagonist effects on the estrogen receptor (ER). It is an estrogen antagonist in the breast regardless of pre- or postmenopausal status, but it is also an estrogen agonist in bone. In postmenopausal women, TMX protects against bone loss [5,6] with a 32% relative risk (RR) reduction in fractures compared with placebo. In contrast, TMX decreases BMD in premenopausal women, even if they maintain regular menstrual cycles [11-12].

AIs such as letrozole, anastrozole, and exemestane block the conversion of androgens to estrogen, primarily in adipose tissue, by inhibiting the aromatase enzyme, thus profoundly lowering serum estrogen levels in postmenopausal women. In premenopausal women, an AI can only be used with surgical or chemical ovarian ablation, since AIs do not affect ovarian estrogen production. In postmenopausal women, adjuvant AIs are superior to TMX and widely used; in these, AIs accelerate bone loss and increase the risk of fracture by about 10% and double (18-20%) after 5 years of treatment. Longer duration of AI therapy is associated with greater increases in fracture risk, with 14% vs 9% in those treated for 10 years vs 5 years, respectively [13-15]. Local Rt interrupts the vascular supply to bone and directly contributes to hypoxia, which inhibits osteoblast function and increases osteoclastogenesis. Specific bone toxicities related to Rt include bone loss within the radiation field, osteopenia or Op, increased risk of fracture, and avascular necrosis [5,6,11-12].

Management of bone health in patients with breast cancer under adjuvant endocrine therapy

All women receiving treatment for BC should be evaluated for their risk of fracture at the onset of Ht, particularly because Op may be a pre-existing condition, there are several specific clinical practice guidelines (CPG) [14]. A clinical history should be taken complete and ideally a dual-energy X-ray absorptiometry (DXA) scan. Emphasis should be placed on a healthy diet and maintaining a normal weight. Adequate intake of dietary protein and natural antioxidants found in fruits and vegetables, rather than supplements, is recommended. We recommend avoiding excess carbohydrates because women with CM with low Ht may have a higher risk of developing diabetes mellitus (DM), which in itself is a risk factor (RF) for fractures; avoid habits that are harmful to bones, smoking, excessive consumption of caffeine, colored carbonated drinks and alcohol [5,16].

The foundation for maintaining bone health includes adequate calcium intake (1,000-1,200 mg daily, preferably from food sources; or adding supplements and vitamin D 800-1,000 units/day for a 25-hydroxycholecalciferol or 25-hydroxyvitamin D level). or cholecalciferol above 30ng/ml, as recommended for the prevention of falls and op fractures in the general osteoporosis population Adequate intake of calcium and vitamin D is important to decrease the risk of hypocalcaemia and maintain bone mineralization when administer antiresorptive therapies [5,17,18].

Adequate weight-bearing and resistance exercise limits bone loss in postmenopausal women with CM [5], although reduction in fracture risk has not been demonstrated [14].

Medications that reduce bone resorption, such as bisphosphonates and denosumab, are widely used and indicated in these women to reduce fracture risk. In postmenopausal women with BC receiving AI therapy, oral bisphosphonates (alendronate, ibandronate, and risedronate) when used for up to 5 years are associated with increases in BMD and reduced risk of fracture14 The addition of zoledronic acid to treatments standard adjuvants in patients with early BC, during a treatment period of 5 years reduces the overall rate of fractures in 6.2 vs. 8.3% of the control group 5. In postmenopausal women in adjuvant treatment with AI the initial use of zoledronic acid (4mg every 6 months) or later use increased BMD, but fracture rates were not statistically different with treatment [5,19,20].

Denosumab, 60mg every 6 months, is approved for women taking AIs at high risk for fracture Op time to first clinical fracture was shown to decrease with denosumab, regardless of baseline BMD or age, and was associated with increased BMD at all skeletal sites [5,21].

Bone assessment in postmenopausal women with breast cancer

The most important thing is the baseline measurement of BMD together with the presence of certain comorbidities that can affect adherence to treatment or increase the risk of adverse events; According to the CPG, medical treatment is recommended in patients with a T-score less than -2.0 or if there are two or more clinical RFs, including Geripausica (> 65 years), low body mass index (BMI (< 20), smoking (current or history), personal history of fracture after 50 years of age, hereditary-family history (AHF) of hip fracture, corticosteroid therapy > 6 months and T score less than -1.5 [14,22]. When T-scores are greater than -2.0 without other RFs, follow-up of bone loss every 1-2 years is reasonable [14], treatment of premenopausal women with antiresorptive therapy is supported if they have undergone ovarian suppression and are receiving AI, with a T-score less than -1.0, or with a prevalent vertebral fracture [5].

In some comorbidities some therapies are not used, for example, bisphosphonates in kidney disease; in severe gastroesophageal reflux disease or dysphagia oral bisphosphonates. Adherence to oral medications is a challenge in the treatment of Op in general. The anabolic agents teriparatide and abaloparatide, and estrogen-containing agents,

should be avoided in patients with BC because they may stimulate the growth of occult or micrometastatic tumor cells and increase the risk of recurrence of BC, a possible increased risk of osteosarcoma in areas exposed to the skeletal Rt. No data are available regarding the efficacy and safety of a combined anabolic and antiresorptive anti-sclerostin antibody (romosozumab) in women with BC [5,23-26].

Risks and benefits of bone health management in breast cancer

A meta-analysis in postmenopausal women with early BC and use of bisphosphonates 5 was associated with a significant decrease in the risk of recurrence, distant recurrence, bone recurrence and mortality from BC and the use of adjuvant bisphosphonates is recommended in these patients who have a high risk of BC recurrence [23], its exact mechanism is unknown. The addition of denosumab to AI and possible anticancer effects reduced the risk of BC recurrence by 18% [5]. However, in high-risk early BC receiving neoadjuvant or adjuvant therapy, adjuvant denosumab (12 mg every 6 months) did not show an effect on disease-free survival (DFS) and overall survival; denosumab is a fully human monoclonal antibody that binds to and inhibits the RANKL receptor activator (TNFSF11) and could affect the biology of BC and could delay bone metastasis or disease recurrence [24].

Bone-directed therapies are very effective in reducing the risk of fractures and, at the same time, are very well tolerated with minimal and generally reversible adverse events [5,11,22], their risk-benefit ratio is highly favorable, regardless of the extremely rare adverse events such as osteonecrosis of the jaw or atypical femoral fractures is associated with other RF such as poor dental and oral hygiene, use of dentures, vitamin D deficiency, corticosteroid therapy or invasive dental procedures such as extractions and post-insertion implants, good oral hygiene and routine dental care are recommended [5,11-13,25]; atypical subtrochanteric femoral fractures may limit the duration of bisphosphonate treatment due to their accumulation in the skeleton, requiring temporary suspension and monitoring for prodromal symptoms that usually precede these fractures [26]. The concern is the increased risk of fracture after denosumab discontinuation; although when evaluating the protective effect of the use of bisphosphonate after denosumab it is the current common practice [5,27-32].

Discussion

The better survival in patients with BC and the better understanding of its carcinogenesis have made bone health key in cancer management. Patients with BC are usually at risk of complications in the skeletal system. The receptor activator of nuclear factor κB ligand (RANKL) inhibitor denosumab and the bisphosphonates zoledronic acid for prevention are approved at lower doses for the treatment of patients with postmenopausal Op, early-stage BC, and weight loss, bone marrow induced by its treatment, mainly caused by AI. Treatment of patients with BC survival is prolonged and long-term treatment with denosumab or bisphosphonates, safety must be considered [26]. The most common cause of bone loss in women is menopause and aging; the risk of osteopenia and Op is higher in women diagnosed with hormone receptor-positive BC, which is probably due to Ht rather than differences in the biology of BC; in BC survivors treated with AI alone or chemotherapy plus AI, they block the aromatase enzyme, resulting in a hypoestrogenic state associated with bone loss; although chemotherapy causes bone loss due to premature menopause in premenopausal women [5-11-12,19-21].

Furthermore, drugs commonly prescribed together with Cht (corticosteroids) are associated with bone loss, it is biologically possible that adjuvant Cht plus Ht have a deleterious effect on bone health early in treatment and incident osteopenia and Op are significantly higher in premenopausal women surviving BC a few years after diagnosis than in women without BC, the risk varies according to cancer treatment; An initial evaluation of BMD and fracture risk close to the diagnosis of BC, prevention strategies and appropriate monitoring can be implemented early, are crucial to prevent fracture risk in order to simultaneously improve quality of life [7-10,16,17,27-32].

Conclusions

Younger BC survivors are at increased risk of osteopenia and Op compared to women without BC. In general, the benefits of antiresorptive agents in women with BC, as well as in the general population of women with Op, greatly outweigh the risks.

References

1. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438-451.
2. Ramin C, May BJ, Roden RBS, et al. Evaluation of osteopenia and osteoporosis in younger breast cancer survivors compared with cancer-free women: a prospective cohort study. Breast Cancer Res. 2018;20(1):134.
3. Lüftner D, Niepel D, Steger GG. Therapeutic approaches for protecting bone health in patients with breast cancer. Breast. 2018;37:28-35.
4. Diana A, Carlino F, Giunta EF, et al. Cancer Treatment-Induced Bone Loss (CTIBL): State of the Art and Proper Management in Breast Cancer Patients on Endocrine Therapy. Curr Treat Options Oncol. 202;22(5):45.
5. Andreopoulou P. Bone Health in Patients with Breast Cancer. Oncol Hematol Rev. 2019;15(1):16–9.
6. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol. 2016;34:611–35.
7. Paschou SA, Augoulea A, Lambrinoudaki I. Bone health care in women with breast cancer. Hormones (Athens). 2020;19(2):171-178.
8. Ramchand SK, Cheung YM, Grossmann M. Bone health in women with breast cancer. Climacteric. 2019:22:6, 589-595
9. Shapiro CL. Osteoporosis: a long-term and late-effect of breast cancer treatments. Cancers (Basel) 2020;12(11):E3094.
10. Mayhew V, Omokehinde T, Johnson RW. Tumor dormancy in bone. Cancer Rep (Hoboken) 2020;3(1):e1156.
11. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO clinical practice guidelines. Ann Oncol. 2020;S0923-7534(20):39995–39996.
12. Diana A, Carlino F, Giunta EF, et al. Cancer Treatment-Induced Bone Loss (CTIBL): State of the Art and Proper Management in Breast Cancer Patients on Endocrine Therapy. Curr Treat Options Oncol. 2021;22(5):45.
13. Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. J Bone Oncol. 2017;7:1–12.
14. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016; 375:209–19.
15. Leslie WD, Morin SN, Lix LM, et al. Performance of FRAX in women with breast Cancer initiating aromatase inhibitor therapy: a registry-based cohort study. J Bone Miner Res. 2019;34(8):1428–1435.
16. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194–1220.

17. Shapiro CL, Van Poznak C, Lacchetti C, et al. Management of osteoporosis in survivors of adult cancers with nonmetastatic disease: ASCO clinical practice guideline. J Clin Oncol. 2019;37(31):2916–46.
18. Pedersini R, Amoroso V, Maffezzoni F, et al. Association of fat Body Mass with Vertebral Fractures in postmenopausal women with early breast Cancer undergoing adjuvant aromatase inhibitor therapy. JAMA Netw Open. 2019;2(9):e1911080.
19. Perrone F, De Laurentiis M, De Placido S, Orditura M, Cinieri S, Riccardi F, et al. Adjuvant zoledronic acid and letrozole plus ovarian function suppression in premenopausal breast cancer:HOBOE phase 3 randomised trial. Eur J Cancer. 2019;118:178–86.
20. Coleman R, Finkelstein DM, Barrios C, et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020;21(1):60–72.
21. Cianferotti L, Bertoldo F, Carini M, et al. The prevention of fragility fractures in patients with non-metastatic prostate cancer: a position statement by the international osteoporosis foundation. Oncotarget. 2017;8:75646–63
22. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone- modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35:2062–81.
23. Nicolatou-Galitis O, Schiødt M, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(2):117–135.
24. Cianferotti L, Bertoldo F, Carini M, et al. The prevention of fragility fractures in patients with non-metastatic prostate cancer: a position statement by the international osteoporosis foundation. Oncotarget. 2017;8:75646–63.
25. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res. 2018;33:190–8.
26. Bone HG, Wagman RB, Brandi ML,et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017;5:513–23.
27. Leder BZ, Tsai JN, Jiang LA, Lee H. Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: the denosumab and teriparatide follow-up study (DATA-Follow-Up). Bone. 2017;98:54–8.
28. McClung MR, Wagman RB, Miller PD, et al. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int. 2017;28:1723-32.
29. Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. Osteoporos Int. 2017;28:3067.
30. ClinicalTrials.gov Identifier: NCT02499237. Zoledronic Acid to Maintain Bone Mass After Denosumab Discontinuation (AfterDmab).
31. Abdel-Razeq H, Al-Rasheed U, Mashhadani N, et al. The efficacy of a comprehensive bone health program in maintaining bone mineral density in postmenopausal women with early-stage breast cancer treated with endocrine therapy: real-world data. Ir J Med Sci. 2022;10.1007/s11845-021-02897-5.
32. Brown KA, Andreopoulou E, Andreopoulou P. Endocrine Therapy-related Endocrinopathies-Biology, Prevalence and Implications for the Management of Breast Cancer. Oncol Hematol Rev. 2020;16(1):17-22.