Management of bone loss in postmenopausal breast cancer patients treated with aromatase inhibitors

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ACTA REUMATOL PORT. 2015;40:323-330

ABSTRACT

Breast cancer is the most commonly diagnosed cancer among women, but despite survival rates improvement, it is still the second major cause of cancer related death. In postmenopausal women with estrogen receptor (ER) dependent breast cancer, hormone therapy is an option, either by direct inhibition of ER using tamoxifen or by aromatase inhibition, resulting in decreased estrogen production. In this paper these two endocrine therapy approaches are compared in terms of their impact on bone health. Guidance for the prevention of bone loss and occurrence of fractures in postmenopausal women receiving AIs is also proposed. Despite intervention strategies to maintain bone health in AI-treated patients are not well established, recommendations by international societies to identify women with high risk of fracture and advice on the preventive anti-fracture therapy are exposed. Finally, available therapeutic options for management of bone loss in patients receiving AIs are presented. The search strategy for this literature review was conducted by using the key words "aromatase inhibitor*" and "bone loss" OR "aromatase inhibitor*" and "osteoporosis" in the MEDLINE/PubMed database. Nowadays, hormone-responsive breast cancer in postmenopausal women is preferably being treated with AIs instead of tamoxifen, due to clear benefits in disease-free survival and reduced recurrence. AIs have an advantageous side effect profile compared to tamoxifen, however all AIs have detrimental long-term effects on bone, due to nearly complete depletion of estrogens, resulting in increased bone loss and increased risk of fracture. Current recommendations state that all women treated with AIs should be evaluated for their fracture risk prior to initiation of AI-treatment, taking in consideration individual bone mineral density and several risk factors. The thresholds to introduce preventive therapy and drugs proposed differ among the available recommendations. Lifestyle modifications and adequate calcium and vitamin D supplementation have been documented to have good impact in long-term bone health. Additionally, bisphosphonates are the first therapeutic option for AI induced bone loss and should be continued as long as AI-treatment is maintained, being iv zoledronic acid 4mg every 6 months the best tolerated option.

Keywords: Osteoporosis; Bone loss; Aromatase inhibitors; Breast carcinoma.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in females and it is expected that 1:8 women will develop breast cancer in their lifetime. Despite survival rates have improved, it is still the second major cause of cancer-related death[1]. From all breast cancer cases, about two thirds are hormone-dependent[2], meaning that either estrogen receptor (ER), progesterone receptor (PR) or both are expressed by tumor cells[3]. Endocrine therapy is an option in the adjuvant treatment and can be achieved by two different mechanisms: 1) preventing cancer cells to interact with ER using selective estrogen receptor modulators (SERMs) and 2) inhibiting the peripheral tissue conversion of androgens into estrogens with aromatase inhibitors (AIs).

Advances in breast cancer treatment of postmenopausal women have led to long-term survival impro-

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vement. For decades, tamoxifen has been the standard of care for the adjuvant treatment of breast cancer[4]. At present, AIs have shown a better overall response and reduced risk of recurrence in postmenopausal women with breast cancer when compared to tamoxifen[4-6]. With the increasing use of AI as an alternative to tamoxifen, the side-effect profile of AIs vs tamoxifen has to be considered in what concerns health and quality of life. In fact, there are overlapping side-effects with some important differences. The consequences of AI--adjuvant treatment of postmenopausal women in bone health are addressed. This paper also aims to provide updated guidance integrating the most relevant and current recommendations of international societies and experts' opinions to identify subjects at increased risk of fracture and the therapeutic strategies to prevent bone loss in postmenopausal patients under adjuvant treatment of breast cancer with AIs.

SEARCH STRATEGY

A literature review was conducted selecting studies using the electronic database MEDLINE/PubMed. The database was searched up to 31st August 2014 and the following key words were applied: "aromatase inhibitor*" and "bone loss" OR "aromatase inhibitor*" and "osteoporosis". The title and abstract of studies were scanned to exclude irrelevant studies for this review. Papers published in English or Portuguese were included and animal studies were excluded. Additional studies were identified from the reference list of all articles retrieved from computerized search. The first author made the search and both authors read the identified relevant articles.

ENDOCRINE THERAPEUTIC OPTIONS FOR ADJUVANT TREATMENT OF BREAST CANCER

For decades, therapy with tamoxifen (a SERM) for a period of 5 years has been considered the gold standard therapy for hormone-dependent breast cancer, with 39% reduction in relapse risk and 24% reduction in mortality risk[6]. Particularly in patients with axillary lymph node involvement, tamoxifen use was associated with a reduction in global mortality risk[5,6]. However, there are two important facts that should be taken into consideration when using tamoxifen: firstly, about 30% of hormone-dependent breast cancers are primarily resistant to tamoxifen and it is expectable that around 40% will develop resistance[7,8] and secondly, the use of tamoxifen is associated with higher incidence of thromboembolic events and increased risk of developing uterine cancer[9,10].

Aromatase inhibitors block the last step in estrogen biosynthesis by inhibiting the cytochrome P-450 enzyme, aromatase, responsible for the peripheral conversion of androgens to estrogens[11]. AIs are classified into type 1 inhibitors, steroidal analogues of androstenedione that irreversibly bind to the active site of aromatase, and type 2 inhibitors, non-steroidal compounds that reversibly bind to the heme group of aromatase[12,13]. Three generation of AIs were developed, being the members of the third generation better tolerated and higher selective for aromatase. The third generation AIs are anastrozole, letrozole, and exemestane and a recent meta-analysis showed comparable anti--tumor efficacy among the three drugs. Several studies comparing AIs with tamoxifen in postmenopausal breast cancer patients showed significant overall response, disease-free survival and reduction of recurrence risk for AIs, making them suitable as first-line hormonal therapy in these women[5,6,14-17,27]. Different studies were also performed in order to understand if there is any benefit on sequential hormone-therapy with AIs after 2-3 years of tamoxifen for a total of 5 years of endocrine therapy compared to 5-years of tamoxifen monotherapy[15,18]. These studies revealed that 5-years sequential therapy is a comparable alternative to tamoxifen monotherapy,[15,18] showing that there is no benefit of combining SERMs with AIs[15,19-22]. However, in the MA-17 study, all disease-free women which have completed 5-years of adjuvant tamoxifen, benefit from an additional period of five years with letrozole[21]. Furthermore, The ATLAS trial showed incremental benefit for 10 years than 5-years treatment with tamoxifen, with lower risk of late recurrence and lower risk of death[23]. Now, that a benefit of extended adjuvant endocrine therapy has been reported, ongoing studies to assess advantage of extended AI-adjuvant therapy beyond 5-years are taking place[24].

AROMATASE INHIBITION INDUCED BONE LOSS

A major concern in AI-adjuvant treatment is the marked decline in estrogen levels, which might be implicated in increased bone loss and fracture risk[25-27]. The bone loss rate of AI -treated postmenopausal women

with breast cancer is higher when compared to postmenopausal women without breast cancer (1-2% vs 2.5% a year)[28,29]. Another study revealed that the number of cases of reduced BMD in postmenopausal women with breast cancer compared with a group of healthy postmenopausal women is higher in the first group[30]. The majority of studies with breast cancer postmenopausal women to assess the consequence of AI adjuvant therapy on bone were conducted in comparison to tamoxifen. Some studies have shown that AIs are responsible for accelerated bone loss (lumbar spine BMD and total hip BMD decrease) and increased fracture incidence, whereas tamoxifen has been associated with bone protection[6,14,31,32]. Despite knowledge of baseline BMD status is of major importance and most patients are clinically diagnosed as osteopenic or osteoporotic, only a small percentage of women which were enrolled in the IES (International Exemestane Group)[33], ATAC[6] or BIG 1-98 (Breast International Group)[34] trials were reported as so, before initiating AI adjuvant therapy. A recent prospective cohort study of postmenopausal breast cancer patients receiving AIs reinforces the need for accurate evaluation of bone health before initiating AI adjuvant therapy as significant prevalence of osteopenia (60.1%), osteoporosis (22%) and fracture (11.4%) at baseline, was reported[35]. Although the absolute fracture rates were diverse among trials, an approximately 1.5% higher risk of fracture in different large AI trials was reported for all three AIs, anastrazole[6,32], letrozole[34,21] and exemestane[14], in comparison to tamoxifen. For bone health maintenance is it believed that the strategy of AI-treatment (monotherapy, sequential) and the duration of treatment (5-years or extended) is more important than the specific drug option[28]. Furthermore, all three AIs, anastrazole, letrozole and exemestane, showed significant enhancement of bone turnover markers, respectively in the ATAC substudy[29], MA.17 bone substudy[20,36] and IES substudy[33,37].

AIs are associated with accelerated bone loss and increased incidence of fractures, whereas tamoxifen has shown to have protective effects on bone due to its partial estrogen-agonist activity. This effect is most apparent in the trabecular bone and has been associated with decreased bone resorption and formation, which results in favorable effects on bone health and decline in the incidence of fractures[38-41]. However, any beneficial effect that tamoxifen therapy might produce on bone ceases once treatment is stopped and it does not occur before menopause[42]. In the IES study, a group of breast cancer patients were treated with prolonged tamoxifen-therapy, whereas another group changed from tamoxifen to exemestane during the study. Women that stayed in tamoxifen had comparable BMD levels from baseline, but those who switched from tamoxifen to exemestane had increased bone loss[33]. Theoretically, we could expect that the steroidal AIs had fewer side effects on bone in comparison to the non-steroidal compounds due to their weak androgenic activity, which is consistent with the results obtained in a study showing BMD reduction at lumbar spine and total hip, respectively, both for exemestane (-4% and -2%) and letrozole (-5.3% and -3.6%).

At menopause, the decline in estradiol serum levels is responsible for an increase in serum bone resorption markers, such as C-telopeptidase (CTX), N-telopeptidase (NTX) and the reduction of bone formation markers, as bone specific alkaline phosphatase (bAP), N-terminal propeptide of procollagen type I (P1nP), osteocalcin (OC). Bone resorption markers and bone formation markers levels were also increased in breast cancer postmenopausal patients treated with any of the three third generation AIs, exemestane[43], anastrazole[29,44], and letrozole[44], while for patients receiving tamoxifen, a decrease in bone turnover biomarkers was observed[44]. Although several studies have shown higher bone turnover biomarkers serum levels in AIs-treated patients in comparison to tamoxifen-treated patients, there is no indication for using bone biomarkers to recognize women at increased fracture risk in clinical practice.

RISK ASSESSMENT AND FRACTURE PREVENTION IN AI-TREATED PATIENTS

Considering the widespread use of estrogen-suppressive therapies in breast cancer patients, it is of great importance to find strategies to overcome the deleterious effects of prolonged AI-therapy. Therefore, it is of major importance to identify patients at risk of increased fracture and define which patients receiving AI treatment should undergo fracture-preventive treatments. The overall fracture risk may be determined taking in consideration the individual BMD loss (by DXA examination at lumbar spine/hip) and several risk factors such as age, smoking, alcohol intake, family history of fracture, previous fragility fracture, corticosteroid therapy, diseases or anticancer therapies that may contribute to impaired bone health. The World

Health Organization Fracture Risk Assessment (FRAX) Tool algorithm is a key development in predicting risk fracture. However it does not take into consideration significant risk factors such as number of previous fractures, physical inactivity, risk for fall and insufficient nutritional intakes, which result in underestimation of fracture risk[45]. Additionally, "secondary osteoporosis" may comprise several circumstances that if occurring concomitantly will also be under-evaluated. Moreover, during active treatment, AIs are expected to have a higher effect on fracture risk which will be underestimated considering the "secondary osteoporosis" in the FRAX tool. For this reason, FRAX remains limited to assess baseline fracture risk in women about to start AIs therapy[46-48].

Currently, there are several therapeutic options approved for osteoporotic fractures prevention in postmenopausal women that have also been proposed for the management of aromatase inhibition induced bone loss. In this paper, international recommendations regarding the identification of women at risk of fracture and pharmacologic interventions for the prevention and treatment of AI-associated bone loss in postmenopausal women with breast cancer will be elucidated[49]. In 2003, the American Association of Clinical Oncology (ASCO) proposed orientations regarding this subject, stating that all patients with a T-score below -2.5 should be treated with bisphosphonates to prevent fractures, whereas the decision to treat patients with T-score between -1 and -2.5, should in an individual basis[50]. The optimal duration of anti-resorptive treatment was not elucidated, but few years later, a study suggested that bone-protective treatment should to be continued at least 2 years, or possibly as long as the AI-therapy is maintained[51]. These guidelines also recommended that all postmenopausal women with breast cancer should have their BMD evaluated before starting AI therapy and that BMD should be re-evaluated and their fracture risk status reassessed after 1-2 years of treatment, either if they are receiving anti--osteoporotic treatment or not[51,52]. A UK expert group[53] recommended that women with BMD <-2.0 or, alternatively, with a T-score between -1.0 and -2.0 and a vertebral fracture, bone loss higher than 4% a year or one or more risk factors should receive anti-resorptive therapy, namely bisphosphonates. Moreover, those with at least one risk factor and over 75 years should be treated with a bisphosphonate, regardless of BMD value. Risk factors for osteoporotic fracture included previous fragility fracture above the age of 50 years; parental history of fracture; body mass index (BMI) of <22; alcohol consumption, corticoid therapy for at least 6 months and diseases known to increase bone fracture[53]. European guidelines, state that all women treated with AIs should be evaluated for risk factors for bone fracture whereas baseline fracture risk should be assessed by performing a DXA examination on hip/spine. Women with a T-score hip/spine <-2.5 or ≥1 prevalent fragility fracture, women over 75 years independently of BMD or with a T-score <1.5 + 1 or more clinical factor risk or a T-score <-1 + 2 or more clinical risk factors should be treated for the entire period of AI treatment with zoledronic acid 4mg i.v. every 6 months, denusomab or alternatively oral bisphosphonates. Additionally, women with a FRAX determined 10-year hip fracture probability over 3% should also undergo anti-resorptive therapy[47]. Additionally, it is recommended that physical activity should be increased and that patients should receive vitamin D (a dose of up to 10000IU/week or 800IU/ /day) and calcium (at least 1000mg/day) supplementation[47].

THERAPEUTIC OPTIONS FOR MANAGEMENT OF BONE LOSS IN PATIENTS RECEIVING AIS

LIFESTYLE MODIFICATIONS, CALCIUM AND VITAMIN D

Lifestyle modifications in what concerns smoking avoidance and regular exercise are of great importance to preserve bone health[50]. Despite evidence is limited to few small trials, it appears that regular exercise may help slow down bone loss in postmenopausal women with breast cancer[51]. Vitamin D at a dose of 482--770IU/day has been documented to be effective in decreasing non-vertebral (20%) and hip fractures (18%) in women over 65 years in a meta-analysis of randomized controlled trials[54]. It is also known that breast cancer patients often have lower levels of vitamin D compared to age-matched healthy women[28]. For that reason, PTH, calcium and 25-OH-vitamin D blood levels are also a key issue and should be evaluated before initiating AI adjuvant treatment of breast cancer to detect vitamin D deficiency and to exclude cases of hyperparathyroidism[35,55]. Despite association between vitamin D serum levels and breast cancer incidence and mortality risk is not well clarified, different studies recommend an intermediate level of vitamin D, showing that both too low and too high levels of vitamin D should be avoided[47]. In conclusion, calcium and vita-

min D, if not contraindicated (eg. patients with hipercalcemia), should be initiated in patients with low vitamin D levels receiving AIs[56] and based on recent guidelines, a 10.000 IU dose of vitamin D/ per week and 1000mg calcium/day are recommended in women with breast cancer[57].

BISPHOSPHONATES

Alendronate, risedronate, ibandronate and zoledronic acid (ZA) are the most used agents for osteoporosis prevention and benefits are clearly demonstrated by the risk reduction of vertebral fracture by 30-70% in osteoporotic patients[58]. The use of these drugs have been extended to help in the management and prevention of AI-associated bone loss[51,59-66]. Although oral bisphosphonates have shown to effectively treat bone loss in women with breast cancer, there is no data on how this translate to fracture reduction in women treated with AIs[63,65,66]. Oral bisphosphonates have problems related to bioavailability, compliance to the treatment and, occasionally, gastrointestinal intolerance that may impair optimal treatment[27]. Switching from oral to i.v. bisphosphonates might be an alternative to overcome these problems and is indicated when patients have an unsatisfactory adherence to the therapy or when a decrease in bone mass density (BMD) is observed after 1-2 years on oral bisphosphonates[51]. ZA, an intravenous bisphosphonate, has shown to be a good option for osteoporosis treatment and to prevent bone metastasis complications[67]. The preventive effect of ZA in letrozole-induced bone loss in breast cancer patients was documented in three randomized international studies, Z-FAST, ZO-FAST and E-ZO--FAST[59,68,69]. The Z-FAST protocol included administration of letrozole in combination with ZA initiated in two different moments: ZA starting at randomization and postponed ZA (initiated after the occurrence of a non-traumatic fracture or when a decrease of -2 in the T-score was recognized). It was demonstrated that long-term administration of letrozole in association with ZA at a dose of 4 mg every 6 months is well tolerated and that ZA should be administered at the time of initiation of AI therapy[60]. The ZA bone protective effect was demonstrated by increased BMD in total hip and lumbar spine, evaluated in an annual basis. This protective effect was independent of T-score before starting AI treatment, chemotherapy or number of risk factors implicated in enhanced risk of bone loss[4,59,68]. Likewise, the results from the ZO-FAST study demonstrated that ZA is associated with a significant increase in BMD in AI-treated patients and that up-front therapy is preferred over delayed scheme[68]. It should be noted that despite BMD increase in ZA treated patients, no difference in fracture incidence was observed when comparing the upfront or delayed therapy scheme with ZA[68]. Furthermore, ZA showed to have long-lasting effects. As documented in this study, two years after stopping treatment, a sustained improvement in BMD was observed in patients treated with ZA when compared to baseline BMD, whereas patients not receiving ZA showed a decrease in BMD from baseline.

In what regards time interval for BMD evaluation, an international expert group indicated that BMD should be evaluated every 1-2 years in all patients receiving AIs with a T-score >-2 and no risk factors associated to bone loss. All subjects having a T-score below -2 and all patients with at least two of the following risk factors: T-score < -1.5, age > 65 years, BMI < 20 Kg/m2, smoking, oral corticosteroid therapy >6 months duration, family history of hip fracture and personal history of fragility fracture after 50 years should undergo bone protective therapy. BMD should be monitored every two years. The suggested treatment should be continued during all extension of AI-treatment and include calcium, vitamin D and zoledronic acid 4mg every 6 months[51].

Apart from the well documented ZA favorable effects in bone health, recent studies also indicate that ZA is responsible for antitumor activity. Several mechanisms may contribute to this effect, namely induction of tumor cell apoptosis, inhibition of cell proliferation and migration, synergism with cytotoxic chemotherapy and anti-angiogenic action[2,68]. Finally, both oral and intravenous bisphosphonates have shown to reduce the risk of breast cancer recurrence in pre-and post-menopausal women[59 68].

SERMs

SERMs, such as tamoxifen and raloxifene, bind with high affinity to ER receptors, exerting agonist activity in bone that is implicated in suppression of bone remodeling[28]. Tamoxifen provides only modest protection against bone loss and fracture risk, being raloxifen the only SERM that is approved for the treatment of osteoporosis in postmenopausal women and solely indicated for women which are not receiving tamoxifen, due to the possible cross-resistance that might occur[50]. Additionally, there is no evidence to recommend the use of raloxifene in the adjuvant treatment of breast cancer with AI[6].

TERIPARATIDE

Teriparatide, a recombinant human parathyroid hormone analog, has shown to be effective in decreasing fracture incidence in osteoporotic men and women and can be used as an alternative to biphosfonates when they are not tolerated or when its use is contraindicated[70]. However, teriparatide is associated with enhanced risk of osteosarcoma, particularly in patients exposed to radiation therapy to the skeleton[71]. In this literature review no reference to the use of teriparatide to control bone loss induced by AIs was found.

DENOSUMAB

Denosumab is a human monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand (RANKL), an important mediator of osteoclast formation, which has recently been developed as a new targeted bone therapy[52]. A recent study demonstrated that denosumab significantly increased BMD in AI-treated patients compared to placebo, however the reduction in cancer recurrence was not observed as with ZA[67]. In a large randomized study, denosumab was more effective at preventing skeletal related events in patients with bone metastases from solid tumors, when compared ZA[72].

CONCLUSION

Recently, long-term adjuvant aromatase inhibition became the gold standard for treatment of hormone-responsive breast cancer, due to superior disease-free survival comparing to tamoxifen. Generally, AIs have a favorable side-effect profile compared to tamoxifen, however bone loss is a chief concern in AI adjuvant treatment because it is associated with increased risk of fractures. Existing guidelines from international societies and expert panels for prevention of aromatase induced bone loss recommend the use of anti-resorptive therapy in postmenopausal women receiving AI-therapy and are unanimous in considering that it is essential to evaluate individual BMD (preferably in total hip or lumbar spine), before initiation of therapy. However, the T-score cut-offs for initiation of osteoporotic therapy whereas the identified risk factors associated with enhanced risk of osteoporosis vary among guidelines.

Strategies that may have a positive impact in long-term bone health in postmenopausal AI-treated patients include lifestyle modifications and adequate calcium and vitamin D supplementation. Bisphosphonates (oral or iv) are effective in preventing BMD loss in postmenopausal women treated with AIs. The strongest data available in terms of number of patients and time of follow up, recommend that patients at risk of accelerated bone loss should be treated with 4 mg intravenous ZA every 6 months. The duration of anti-resorptive therapies should be as long as that of AI administration and BMD should be re-evaluated and fracture risk status reassessed after 1-2 years of treatment. In addition to the effective positive effects on bone, there is now evidence of the anticancer benefits of ZA.

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REFERENCES

1. Alteri R, Barnes C, Burke A, et al. Breast Cancer Facts & Figures 2013-2014. American Cancer Society 2013.
2. Bauer M, Bryce J, Hadji P. Aromatase inhibitor-associated bone loss and its management with bisphosphonates in patients with breast cancer. Breast Cancer (Dove Med Press) 2012;4:91-101.
3. Rugo HS. The breast cancer continuum in hormone-receptor--positive breast cancer in postmenopausal women: evolving management options focusing on aromatase inhibitors. Ann Oncol 2008;19:16-27.
4. Oyan B. Potential role of bone-directed therapy on the superiority of aromatase inhibitors over tamoxifen. Med Hypotheses 2011;77:1028-1030.
5. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27—a randomized controlled phase III trial. J Clin Oncol 2013;31:1398-1404.
6. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60-62.
7. Riggins RB, Schrecengost RS, Guerrero MS, Bouton AH. Pathways to tamoxifen resistance. Cancer Lett 2007;256:1-24.
8. Ring A, Dowsett M. Mechanisms of tamoxifen resistance. Endocr Relat Cancer 2004;11:643-658.
9. Fendl KC, Zimniski SJ. Role of tamoxifen in the induction of hormone-independent rat mammary tumors. Cancer Res 1992;52:235-237.
10. Vancutsem PM, Lazarus P, Williams GM. Frequent and specific mutations of the rat p53 gene in hepatocarcinomas induced by tamoxifen. Cancer Res 1994;54:3864-3867.
11. Joensuu H, Ejlertsen B, Lonning PE, Rutqvist LE. Aromatase inhibitors in the treatment of early and advanced breast cancer. Acta Oncol 2005;44:23-31.
12. Goss PE, Strasser K. Chemoprevention with aromatase inhibitors – trial strategies. J Steroid Biochem Mol Biol 2001;79:143--149.
13. Janicke F. Are all aromatase inhibitors the same? A review of

the current evidence. Breast 2004;13 Suppl 1:S10-18.
14. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007;369:559-570.
15. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081-1092.
16. Xu HB, Liu YJ, Li L. Aromatase inhibitor versus tamoxifen in postmenopausal woman with advanced breast cancer: a literature-based meta-analysis. Clin Breast Cancer 2011;11:246-251.
17. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010;28:509-518.
18. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 2006;17 Suppl 7:vii10-14.
19. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 2003;98:1802-1810.
20. Goss PE. Letrozole in the extended adjuvant setting: MA.17. Breast Cancer Res Treat 2007;105 Suppl 1:45-53.
21. Goss PE, Ingle JN, Martino S, 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 2005;97:1262-1271.
22. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 2006;7:991-996.
23. Obiorah I, Jordan VC. Progress in endocrine approaches to the treatment and prevention of breast cancer. Maturitas 2011;70: 315-321.
24. Fontein DB, Nortier JW, Liefers GJ, et al. High non-compliance in the use of letrozole after 2.5 years of extended adjuvant endocrine therapy. Results from the IDEAL randomized trial. Eur J Surg Oncol 2012;38:110-117.
25. Rinaldi RZ. Aromatase inhibitor adjuvant chemotherapy of breast cancer results in cancer therapy induced bone loss. Curr Osteoporos Rep 2013;11:61-64.
26. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1998;339:733-738.
27. Becker T, Lipscombe L, Narod S, Simmons C, Anderson GM, Rochon PA. Systematic review of bone health in older women treated with aromatase inhibitors for early-stage breast cancer. J Am Geriatr Soc 2012;60:1761-1767.
28. Coleman RE, Body JJ, Gralow JR, Lipton A. Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. Cancer Treat Rev 2008;34 Suppl 1:S31-42.
29. Eastell R, Hannon RA, Cuzick J, 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 2006;21:1215-1223.
30. Conde DM, Costa-Paiva L, Martinez EZ, Pinto-Neto AM. Bone mineral density in postmenopausal women with and without breast cancer. Rev Assoc Med Bras 2012;58:673-678.
31. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol 2008;26:1051-1057.
32. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455--462.
33. Coleman RE, Banks LM, Girgis SI, 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 2007;8:119-127.
34. International Breast Cancer Study G, Colleoni M, Gelber S, et al. Effects of a treatment gap during adjuvant chemotherapy in node-positive breast cancer: results of International Breast Cancer Study Group (IBCSG) Trials 13-93 and 14-93. Ann Oncol 2007;18:1177-1184.
35. Servitja S, Nogues X, Prieto-Alhambra D, et al. Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer. Breast 2012;21:95--101.
36. Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629-3635.
37. McCloskey EV, Hannon RA, Lakner G, et al. Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. Eur J Cancer 2007;43:2523-2531.
38. Grey AB, Stapleton JP, Evans MC, Tatnell MA, Ames RW, Reid IR. The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. Am J Med 1995;99:636-641.
39. Chang J, Powles TJ, Ashley SE, et al. The effect of tamoxifen and hormone replacement therapy on serum cholesterol, bone mineral density and coagulation factors in healthy postmenopausal women participating in a randomised, controlled tamoxifen prevention study. Ann Oncol 1996;7:671-675.
40. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652-1662.
41. Seeman E. Pathogenesis of bone fragility in women and men. Lancet 2002;359:1841-1850.
42. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996;14:78-84.
43. Goss PE, Hadji P, Subar M, Abreu P, Thomsen T, Banke-Bochita J. Effects of steroidal and nonsteroidal aromatase inhibitors on markers of bone turnover in healthy postmenopausal women. Breast Cancer Res 2007;9:R52.
44. McCaig FM, Renshaw L, Williams L, et al. A study of the effects of the aromatase inhibitors anastrozole and letrozole on bone

metabolism in postmenopausal women with estrogen receptor-positive breast cancer. Breast Cancer Res Treat 2010;119: 643-651.
45. Dhesy-Thind SK. Screening for osteoporosis in postmenopausal women with breast cancer receiving aromatase inhibitors: less is more? J Clin Oncol 2012;30:1408-1410.
46. Body JJ. Increased fracture rate in women with breast cancer: a review of the hidden risk. BMC Cancer 2011;11:384.
47. Rizzoli R, Body JJ, DeCensi A, 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 2012;23:2567-2576.
48. Tavares V, Canhão H, Gomes JAM, et al. Recomendações para o diagnóstico e terapêutica da osteoporose. Acta Reumatologica Portuguesa 2007;32:49-59.
49. Hong S, Didwania A, Olopade O, Ganschow P. The expanding use of third-generation aromatase inhibitors: what the general internist needs to know. Journal of General Internal Medicine 2009 2009;24:383-388.
50. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042-4057.
51. Hadji P, Body JJ, Aapro MS, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol 2008;19:1407-1416.
52. Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol 2011;22:2546-2555.
53. Reid DM, Doughty J, Eastell R, 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 2008;34 Suppl 1:S3-18.
54. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:551-561.
55. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266--281.
56. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol 2000;18:1570--1593.
57. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-1930.
58. Reginster JY. Antifracture efficacy of currently available therapies for postmenopausal osteoporosis. Drugs 2011;71:65-78.
59. Brufsky AM, Bosserman LD, Caradonna RR, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. Clin Breast Cancer 2009;9:77-85.
60. Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. Cancer 2012;118:1192-1201.
61. Hines SL, Sloan JA, Atherton PJ, et al. Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy. Breast 2010;19:92-96.
62. Logman JF, Heeg BM, Botteman MF, Kaura S, van Hout BA. Economic evaluation of zoledronic acid for the prevention of osteoporotic fractures in postmenopausal women with early-stage breast cancer receiving aromatase inhibitors in the UK. Ann Oncol 2010;21:1529-1536.
63. Markopoulos C, Tzoracoleftherakis E, Polychronis A, 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 2010;12:R24.
64. Schech AJ, Nemieboka BE, Brodie AH. Zoledronic acid inhibits aromatase activity and phosphorylation: potential mechanism for additive zoledronic acid and letrozole drug interaction. J Steroid Biochem Mol Biol 2012;132:195-202.
65. Sergi G, Pintore G, Falci C, et al. Preventive effect of risedronate on bone loss and frailty fractures in elderly women treated with anastrozole for early breast cancer. J Bone Miner Metab 2012;30:461-467.
66. Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol 2010;28:967-975.
67. Body JJ. New developments for treatment and prevention of bone metastases. Curr Opin Oncol 2011;23:338-342.
68. Eidtmann H, de Boer R, Bundred N, 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 2010;21:2188-2194.
69. Llombart A, Frassoldati A, Paija O, 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 2012;12:40-48.
70. Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 2005;16:510-516.
71. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health in Cancer Care. J Natl Compr Canc Netw 2009;7 Suppl 3:S1-32; quiz S33-35.
72. Henry D, Vadhan-Raj S, Hirsh V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 2014;22:679-687.