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REVIEW

Cancer Treatment-Induced Bone Loss in women with breast cancer

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Osteoporosis is one of the most frequent diseases in postmenopausal women, leading to an increased fracture risk due to the physiologic loss of the bone protective effects of estrogen. Hereby, several risk factors for fracture such as prevalent fracture, low bone mineral density (BMD), age, low body mass index, family history, tendency to falls, smoking, use of SSRIs, glucocorticoid use etc. have been identified. In addition, the further reduction in endogenous estrogens with chemotherapy (CHT), GnRH analoga or aromatase inhibitors (AIs) continuously increases fracture risk. Breast cancer (BC) on the other hand is the most frequent cancer type in women. Recent reports indicate a continuous increased incidence, whereas mortality, due to early diagnosis and treatment improvements, is decreasing. Dependent on specific tumor characteristics, radiation, CHT, antibody treatment as well as endocrine treatment have been included into the adjuvant clinical treatment setting. Some but not all of these cancer-specific treatments interfere with bone turnover, leading to an accelerated bone loss referred to as cancer treatment-induced bone loss (CTIBL). Whereas CHT leads to an unspecific increase in bone resorption, AI reduces residual serum endogenous estrogen level and is associated with a decrease in BMD and increased fracture risk. Independent of the type of AI administered, bone loss is 2–3-fold increased compared with healthy, age-matched postmenopausal controls. Therefore, several guidelines have emerged to help managing CTIBL in women with BC including strategies to identify and treat those at highest risk for fractures. This review summarizes the current knowledge on CTIBL and fracturing risk and indicates preventative strategies.

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Introduction

Osteoporosis is one of the most frequent diseases with more than 75 Mio affected in the US, Europe and Japan. Worldwide an estimated nine Mio osteoporosis-related fractures occur annually, of which 4.5 Mio are being documented in the US and Europe. The lifetime risk of sustaining an osteoporosis-related fracture for a postmenopausal woman is estimated at 30–40% in the industrialized countries, which is close to the frequency of coronary heart disease. In the WHO ranking, osteoporosis incidence exceeds hypertension and rheumatoid arthritis and slightly less frequent than diabetes mellitus and chronic obstructive lung disease.[1]

In Germany, based on the results of the Bone Evaluation Study (BEST), 6.3 Mio (5.2 Mio women and 1.3 Mio men) have been diagnosed with osteoporosis in 2009. The annual incidence rate of new cases is estimated at 885 000.[2] The fracture incidence of 51% in osteoporosis patients is considerably higher as assumed in earlier epidemiological studies.[2,3] Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone mineral density (BMD) and bone quality[4]. Osteoporosis is operationally defined on the basis of a BMD measurement by dual x-ray absorptiometry scaled by the *T*-score (-2.5s.d.). Hereby, the *T*-score compares the measured value of an individual to the average of healthy young controls.[1,4] Besides low BMD, several BMD-independent clinical risk factors have been identified and have been validated in large prospective as well as population-based studies in postmenopausal women, significantly influencing treatment intervention thresholds.[5] Hereby, one important risk factor for fracture is cancer treatment-induced reduction in serum endogenous estrogen levels in pre- or postmenopausal women with breast cancer (BC).[6]

BC on the other is the most common cancer type among women.[7] There are about three million women living in the USA

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with a history of invasive BC with BC alone is expected to account for 29% (232.340) of all new cancer cases among women.[7] Current guidelines recommend aromatase inhibitors (AIs) for postmenopausal women with hormone receptor-positive BC at some point during adjuvant treatment, either as up-front therapy or as sequential treatment after tamoxifen.[8,9] In postmenopausal women, the aromatase enzyme is located in the muscle and adipose tissue converting androgen precursors into estrogen.[10] AIs (anastrozole, exemestane and letrozole) block the aromatase enzyme leading to a decrease in circulating serum estrogens and thereby improving disease-free survival as well as overall survival compared with tamoxifen in the adjuvant, as well as in the metastatic setting.[11] However, the oncology wise intended beneficial effect of reducing endogenous estrogens in women with BC leads to an increased bone turnover, bone loss and increased fracture risk.[12]

Bone Physiology and Pathophysiology

During healthy reproductive life, healthy bone is in a constant state of remodeling, an essential process to preserve structural integrity and minimize the risk of fragility fractures.[13] Bone-derived osteoblasts, osteocytes and osteoclasts interact through the influence of cytokines and other humoral factors to couple formation and resorption. In normal health, the relationship between osteoblastic bone formation and osteoclastic bone resorption is finely balanced. With the onset of menopause, this balance is disturbed by the residual decrease in endogenous estrogens. Hereby, women comprise an individually varying discontinuous annual bone loss of 1–5% per year for the first 10–15 years after menopause.[12,14] Thereafter, bone loss seems to decrease further but to a smaller extent.

In the past, clinical risk factors for BC such as early menarche, late menopause, obesity, nulliparous, and advanced age at first birth as well as hormone replacement therapy have been linked with an increased endogen or exogenous estrogen exposure time. These risk factors for BC on the other hand were associated with a decreased risk for cancer treatment-induced bone loss (CTIBL) and fracture incidence [8]. Hereby, circulating sex hormones represent the mediator for the increased risk of BC and preventative factor for CTIBL.[15,16] Estrogens directly influences bone metabolism by estrogen receptors on osteoblasts, osteocytes and osteoclasts and indirectly through cytokines such as transforming growth factor-β, leptin, neuropeptide Y, tumor necrosis factor, insulin-like growth factor-1 and interleukin-1 and -6.[16,17]

However, cancer treatments including GnRH analoga, chemotherapy (CHT) and tamoxifen in premenopausal women as well as CHT and AI in postmenopausal women with BC disturb this balance mainly through reduction in serum endogenous estrogens and result in a loss of the normal structural integrity of the skeleton.[18]

Bone-Related Effects of BC Treatment

Treatment with CHT

CHT such as taxane, doxorubicin, 5-fluorouracil, cyclophosphamide, methotrexate and cisplatin can lead to an increased bone resorption, bone loss and a reduction in bone architecture. In animal models, a 60% reduction in trabecular bone structure has been reported. In addition, CHT can lead to a secondary amenorrhea in premenopausal women with BC, leading to an additional, clinically meaningful increased bone loss due to an increased osteoclast bone resorption.[19–21] In a case–control study with 352 postmenopausal women, a fivefold increased incidence of fractures per year and a 2.8-fold increased relative risk in women with primary BC was observed. Women with recurrent BC showed a sixfold increase in fractures already at the beginning of the study and a 23-fold increased incidence of fractures annually, as well as a 24.5 increased relative risk.[22]

Endocrine treatment

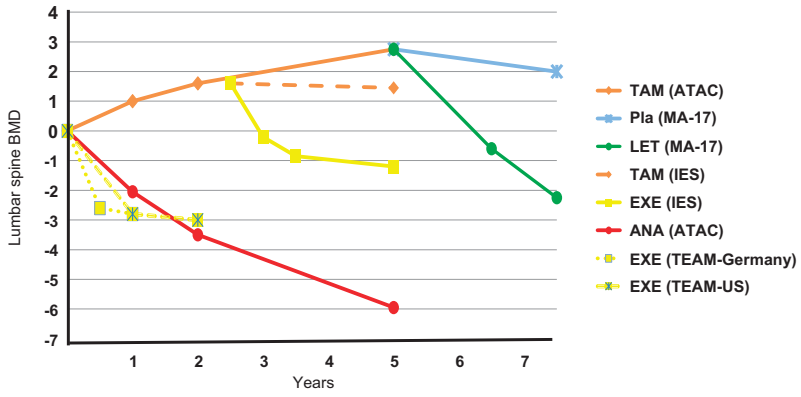
In contrast to premenopausal women, treatment with tamoxifen in postmenopausal women with BC is well known to stabilize or rather increase BMD.[23,24] According to a randomised placebo controlled double-blinded trial, an increase in the BMD in women who received tamoxifen compared with an annual decrease in the control group (0.6% vs 1.0%) has been observed. The same study showed a significant decrease in the incidence of fractures in the tamoxifen-treated women with BC.[23,25] In addition to the increased BMD, a significant improvement of the bone structure was reported.[26,27]

With regard to the mechanism of action, AI inhibits the activity of the aromatase enzyme, leading to a decrease in serum estradiol and thereby decreasing disease-free survival in women with BC.[28] The AI-induced estrogen deficiency leads to a negative bone balance with increased markers of bone resorption, as well as a decreased BMD and increased fracture risk.[29] AI-associated bone loss (AIBL) occurs at a rate of 2–3-fold higher than bone loss in healthy, age-matched postmenopausal controls, resulting in a significant higher incidence of fractures regardless of the AI administered.[12] In addition to the BMD decrease, bone structure assessed by the trabecular bone score (TBS) is also significantly decreased at the lumbar spine after 2 years of an anastrozole treatment.[27] **Figures 1 and 2** summarise the influence of AIs on the BMD and the fracture risk with regard to results of different trials.[6,30–32]

Management of AIBL/CTIBL in Clinical Practice

In the past, the ASCO guidelines were the only bone health guidelines available indicating medical intervention only if BMD was below the given WHO threshold of -2.5SD. More recently, several clinical guidelines have been reported, all recommending that women with BC receiving an AI or ovarian suppression should have their bone health monitored [6]. Because of the well-established BMD-independent risk factors, BMD measurement should not be the sole criterion for determining fracture risk. Overall fracture risk assessment tools using combined risk factors provide the most accurate evaluation. The World Health Organization Fracture Risk Assessment tool (FRAX) algorithm is valid for postmenopausal women and calculates the 10-year fracture risk with or without BMD measurement and includes several fracture-related risk factors, although anticancer treatments are not included as a specific risk factor.[33]

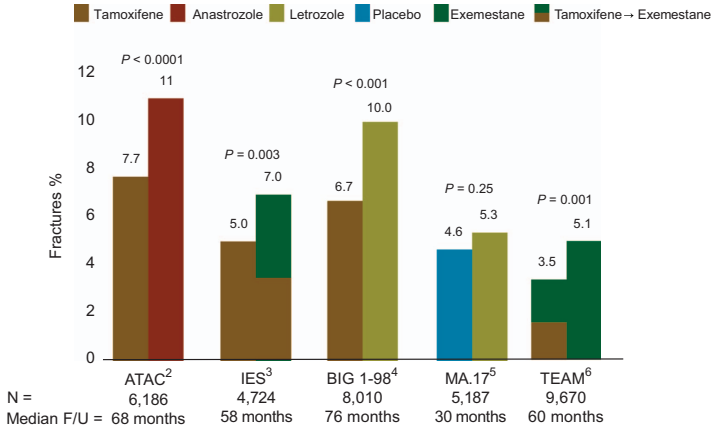
To identify and manage secondary causes of osteoporosis, a comprehensive laboratory assessment is required and should include serum levels of calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone, hemoglobin, C-reactive protein,



ATAC[1] Anastrozole vs tamoxifen upfront,; IES[2] Exemestane vs tamoxifen following switch after 2-3 years tamoxifen; MA-17[3] Letrozole vs placebo following switch after 5 years on tamoxifen,; TEAM[4] Exemestane vs tamoxifen for 2-3 years (before switching from TAM to EXE vs. EXE for 5 years)

1. Howell A, et al.*Lancet* 2005;365:60-62; 2. Coleman RE, et al. *Lancet Oncol.* 2007;8:119-127; 3. Goss PE, et al. *J Natl Cancer inst.* 2005;97:1262-1271; 4.Hadji P, et al. Presented at 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, USA; December 10-14, 2008; Abstract 1143.

Figure 1 Influence of treatment with aromatase inhibitors on the BMD.



F/U, follow-up; NS, not significant; ATAC, Arimidex tamoxifen alone or in combination; IES, intergroup exemestane study; BIG 1-98, breast international group 1-98 collaborative group; TEAM, tamoxifen exemestane adjuvant multinational.

1. Adapted from Hadji P, et al. *US Oncological Disease*. 2007;1:18-21; 2. Howell A, et al. *Lancet*. 2005;365(9453):60-62; 3. Coleman RE, et al. *Lancet Oncol*. 2007;8:119-127; 4. Rqbaglio et al. Ann of Oncologz 2009; may 27th ; 5. Goss PE, et al. *J Natl Cancer Inst*. 2005;97(17):1262-1271; 6. J . Rea D. et al. SABCS 2009, San Antonio, Tex. Abstract 15; 5

Figure 2 Influence of treatment with aromatase inhibitors on the fracture risk.

alkaline phosphatase, thyroid-stimulating hormone, creatinine clearance and protein electrophoresis (serum and/or urine).[18]

In premenopausal women, CHT may induce premature menopause or GnRH -analogs reversibly suppress ovarian function, leading to a reduction in circulating estrogen levels. In addition to bone loss associated with low estrogen levels, cytotoxic CHT may also have a direct negative impact on bone metabolism. Therefore, CTIBL compromises significantly bone health in premenopausal women with BC. Current fracture risk assessments tools are based on data from healthy post-menopausal women and do not adequately address the risks associated with treatments in younger premenopausal women. Guidance from expert groups for premenopausal women with BC has been published and recommend that all premenopausal women be informed about the potential risk of bone loss prior to beginning anticancer therapy with the use of antiresorptives if the BMD *Z*-score is below -2.[19,34]

The first guidelines for the prevention and treatment of AIBL in postmenopausal women with BC, including clinical risk factors $\pm$BMD, emerged in 2008.[34] On the basis of a systematic literature search, an expert group drafted a practical approach for the management of AIBL. In 2011, this guidance was updated with regard to clinical risk factors, as well as the addition of denosumab as a further treatment option.[35] These guidelines recommend antiresorptive treatment in patients receiving AI with a T-score below -2.0 or having two or more clinical risk factors for fracture.[36,37] Recently, the European Society for Medical Oncology (ESMO) confirmed the reported risk factors that increase fracture risk in postmenopausal women with BC. Recommendation level A is assigned for the flow for fracture risk assessment, prevention and treatment of AIBL, which is enclosed in (**figure 3**).[13] However, the guidelines and algorithms base their recommendations on different cut-off points for *T*-score and age, whereas risk factors other than *T*-score are not used uniformly.

Practical Aspects of the Treatment of CTIBL

All patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium-enriched diet and exercise moderately (resistance and weight-bearing exercise).[38,39] Studies on physical activity for

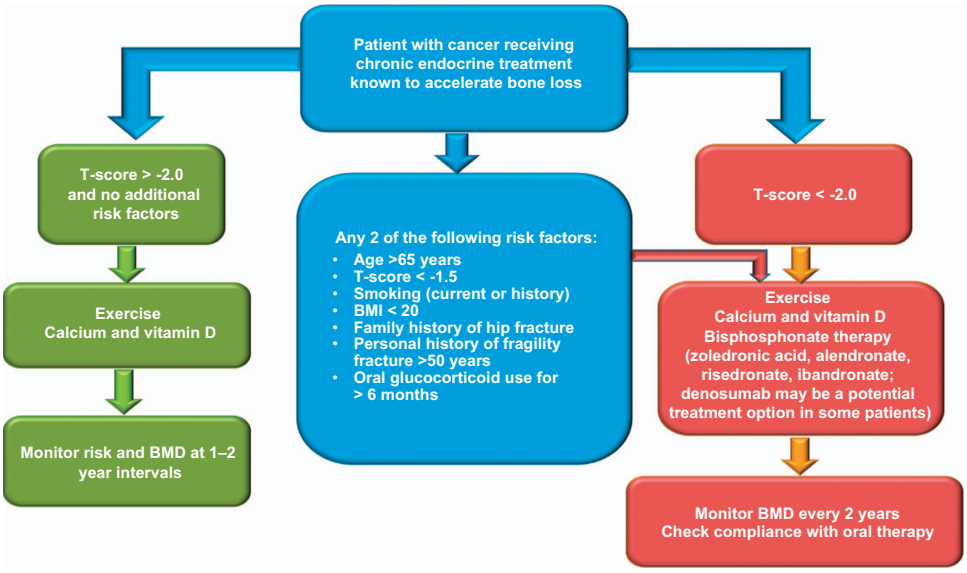


Figure 3 ESMO Clinical Practice Guidelines International guideline for managing bone health during cancer treatment.[13]

osteoporosis prevention have shown diverse results on BMD.[40,41] A case–control study showed a delay in the loss of BMD in 66 pre and postmenopausal women with BC using either aerobic (−0.8%) or weight training (−4.9%) compared with controls.[42] In the current guidelines (ESMO, DVO), the level of evidence and the degree of recommendation arestill low (4/C).[13] Recent reports provided evidence that physical activity carried out 3 h per week decreases the BC-related morbidity and mortality.[43] In addition, lifestyle changes such as reduced alcohol consumption and to quit smoking are recommended.[13]

In the past, numerous study results on the preventative effects of adequate supplementation of vitamin D (1000–2000 units per day) in postmenopausal women with osteopenia/osteoporosis have been reported.[39,41,44] A sufficient long-term intake of calcium had been shown to decrease the risk of osteoporosis for up to 20% [39]. A meta-analysis of 45 studies investigating the influence of a calcium and vitamin D supplementation on hip-fracture rates in elderly individuals living in nursing homes showed a significant risk reduction.[45] Furthermore, these results were confirmed by a second meta-analysis in postmenopausal elderly women and men ($n = 45\,509$) that also reported decreased risk of fracture by 18%.[39] However, it needs to be pointed out that the sufficient intake of Calcium and Vitamin D alone cannot prevent rapid bone loss initiated by AI.

Antiresorptives in the Treatment of CTIBL

Because of the increased fracture risk in women with BC, preventative measures are recommended early in the cause of the disease.[46–48]

A number of antiresorptives are currently recommended for the treatment of osteoporosis, because they have been shown to significantly decrease osteoporosis-related fracture risk, such as vertebral and non-vertebral fractures in RCTs. The overall risk reduction across nine antiresorptives in preventing vertebral fractures was 51% (odds ratio of 0.49; 95% confidence interval: 0.41, 0.58) and 19% (odds ratio of 0.81; 95% confidence interval: 0.77, 0.86) for non-vertebral fractures.[49]

Treatment of AIBL with Bisphosphonates and Denosumab

The data from randomised clinical trials in >5000 patients indicate that bisphosphonates (both intravenous and oral) and denosumab administered at doses and schedules that approximate to those used for the treatment of postmenopausal osteoporosis can prevent bone loss in women with BC.[18,50–55] Although these trials were not designed for a fracture-prevention end point, data from the osteoporosis setting have demonstrated a correlation between BMD improvements and fracture prevention. Therefore, data from the larger studies in this group may be considered as an evidence for preserving skeletal health during therapy.

Conclusion

In conclusion, CTIBL in pre- as well as in postmenopausal women with BC is a frequent side effect of CHT, GnRH-analogs and/or AT treatment. Therefore, several guidelines have emerged to ensure proper management of CTIBL prevention and treatment. Patients who are suggested to receive CHT, GnRH-analogs and/or AI treatment are recommended to be counseled regarding clinical risk factors, monitoring BMD at baseline, physical exercise and calcium/vitamin D supplements. Patients identified with *T*-score ⩾2.0 and no further risk factors should be monitored on the basis of risk factors and estimated BMD loss at 1–2-year intervals. In patients with at least two risk factors for fractures and a *T*-score below −2.0, the initiation of a bone directed treatment including monitoring compliance to treatment is recommended. Further research on tracking guideline adherence, observing the feasibility and practicability of guideline implementation to bridge the gap between determined scientific best evidence and applied best practice, is needed to adjust these guidelines in the future.

Conflict of Interest

PH has received honoraria, unrestricted educational grants and research funding from the following companies: Astra Zeneca, Amgen, Eli Lilly, Novartis, Pfizer, Roche and Wyeth.

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