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Focus On

Bisphosphonates and the prevention of osteoporosis in the adjuvant setting

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Abstract Endocrine adjuvant therapy for breast cancer has been associated with a decrease in bone mineral density (BMD) and bone loss. For aromatase inhibitors, this bone loss is likely to be the most significant limitation to their long-term use. Treatments traditionally used to counteract his effect include exercise and supplementation with calcium and vitamin D. A newer treatment is the use of bisphosphonates, a class of drugs that reduce osteoclast activity. Clinical trials currently underway to examine the effect of bisphosphonate treatment on breast cancer patients have shown improvement in bone strength. Additional benefits of bisphosphonates, currently under study, give this class of drugs an important role to play in the treatment of cancer treatment-induced bone loss.

Keywords: Adjuvant therapy; Bisphosphonates; Breast cancer; Zoledronic acid

Introduction

Adjuvant therapy for breast cancer can be associated with decreased bone mineral density (BMD) that may lead to skeletal morbidity. This is particularly true for modern treatment regimen including aromatase inhibitors, since these agents very effectively reduce peripheral estrogen, thus leading to estrogen deprivation effects on the bone. Severe bone loss has been reported in all trials using aromatase inhibitors. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial reported 11.6% fractures in the anastrozole arm after a follow up of 68 months, compared to 7.7% in the tamoxifen arm [1]. The Breast International Group (BIG) 1-98 trial reported 5.8% fractures in the letrozole arm at a follow up of 26 months, compared to 4.1% in the tamoxifen arm [2]. Thus, both trials result in a – strikingly similar – fracture rate of 22 per 1000 women-years, which can be considered the true bone effect of third-generation aromatase inhibitors in a postmenopausal breast cancer population.

Given that endocrine adjuvant therapy for breast cancer, particularly in the relatively low-risk endocrine-responsive postmenopausal patient population that comprises the majority of patients affected is now to be considered a long-term treatment, the bone problem will likely be the Achilles' heel of these otherwise very effective and generally well-tolerated drugs. While the risk of endometrial cancer limited the long-term us of tamoxifen in the adjuvant and preventive breast cancer setting, treatment-induced bone loss is the most likely limitation of the use of aromatase inhibitors [3].

In any case, patients on long-term aromatase inhibitor treatment should be advised to optimize their lifestyle with regard to prevention and treatment of osteopenia and osteoporosis. Regular physical exercise, preferable outdoors, can prevent deterioration of bone density. Also, many experts advise supplementation with calcium and vitamin D. In addition, in case of treatment-induced osteoporosis, the administration of bisphosphonates may be considered [4].

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Bisphosphonates are a class of drugs that reduce osteoclast activity [5]. Since breast cancer is in many ways related to bone metabolism, bisphosphonates are increasingly used for breast cancer patients. Breast cancer patients suffer for not yet completely understood reasons from osteoporosis multiple times more likely than non-breast-cancer patients, potentially depicting a common endocrine environment for both diseases [6]. In addition, breast cancer frequently metastasizes to the bones, and since bone metastases in many cases have a good prognosis, many patients have to be treated for this for prolonged periods of time. Furthermore, bone pain is frequent in breast cancer patients [7].

Current trials of bisphosphonates

Probably even more importantly in the years to come is the potential use of bisphosphonates in order to treat or prevent cancer treatment-induced bone loss (CTIBL). Currently, the Z-FAST (zometa-femara adjuvant synergy trial) and ZO-FAST trials are investigating the issue of prevention using primary treatment with zoledronic acid vs. treatment of only those affected from severe BMD changes in the most common setting of postmenopausal patients suffering from endocrine-responsive breast cancer and treated with the aromatase inhibitors (AI) letrozole. Interim results after 6 and 12 months have recently been presented [8], indicating that lumbar spine BMD was improved by upfront bisphosphonate use on average by 3.3% after 6 months. In the 'delayed' group, patients had to be treated with zoledronic acid due to crossing the protocol-defined T-score barrier of 2.0 as early as after a median of 6.3 months.

CTIBL also poses a significant challenge in premenopausal breast cancer patients. The magnitude of the bone loss induced by the antioneoplastic treatment may even be more pronounced in younger women than in postmenopausal patients, since the non-physiologic invasiveness of the therapeutic intervention may be even more dramatic. Ovarian ablation using GNRH-analogues is a valid treatment option for premenopausal breast cancer patients with hormone-responsive breast cancer [9], and by itself significantly reduces peripheral estrogen levels. In addition, particularly in younger women, cytotoxic chemotherapy suppresses ovarian function, and – depending on the regimen used – many women will become amenorrhoic permanently following such treatment [10,11].

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) conducted a study addressing the question whether zoledronic acid can prevent bone loss associated with adjuvant standard endocrine therapy in premenopausal patients. ABCSG-12 is a randomized, open-label, phase III, four-arm trial comparing tamoxifen (20 mg/day orally)/goserelin (3.6 mg every 28 days subcutaneously) ± zoledronic acid (4 mg intravenously every 6 months) vs. anastrozole (1 mg/day orally)/goserelin ± zoledronic acid for 3 years in premenopausal women with hormone-responsive breast cancer. In a BMD subprotocol at three-trial centers, patients underwent serial BMD measurements at 0, 6, 12, 24 and 36 months.

401 patients were included in the BMD subprotocol. Endocrine treatment without zoledronic acid led to significant ($P < 0.001$) overall bone loss after 3 years of treatment (BMD, −14.4% after 36 months; mean T-score reduction, −1.4). Overall bone loss was significantly more severe in patients receiving anastrozole/goserelin (BMD, −17.3%; mean T-score reduction, −2.6) compared with patients receiving tamoxifen/goserelin (BMD, −11.6%; mean T-score

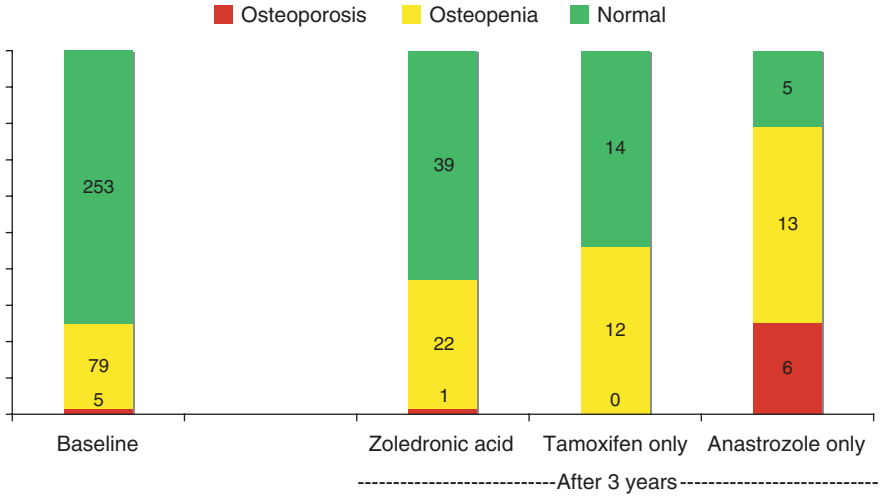

Figure 1.
Patient population of ABCSG-12 according to bone status.

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reduction, −1.1). In contrast, BMD remained stable in zoledronic acid-treated patients ($P < 0.0001$ compared with endocrine therapy alone). No interactions with age or other risk factors were noted. As shown in Figure 1, while 25% of patients treated with anastrozole and goserelin become osteoporotic after 3 years of treatment, there was literally no bone loss in those who were treated with zoledronic acid [12].

The results of the trial indicate that endocrine therapy causes significant bone loss that increased with treatment duration in premenopausal women with breast cancer. Zoledronic acid 4 mg every 6 months effectively inhibited bone loss. Regular BMD measurements and initiation of concomitant bisphosphonate therapy upon evidence of bone loss should be considered for patients undergoing endocrine therapy [4].

The future

There are several bisphosphonates currently available, some of them are administered orally, others via intravenous infusion. With intravenous bisphosphonates, patients' renal function has to be observed and eventually dose reductions must take place [13]. Oral bisphosphonates are often taken with poor compliance due to gastrointestinal side effects [14]. Scientific evidence directly comparing oral and intravenous drugs of different bisphosphonates in a head-to-head comparison is not available, however, several trials are ongoing or being initiated. These issues as well as the optimal duration of therapy, definition of patient subgroups at particular risk for CTIBL, and economically reasonable monitoring of bone loss and treatment effect are yet to be defined by future clinical trials.

In the future, not only breast cancer patients with bone disease will receive bisphosphonates, but more likely also the majority of all breast cancer patients may be candidates for that treatment. In addition to their bone-protective effects, bisphosphonates may exert other antineoplastic actions, including induction of apoptosis and inhibition of neoangiogenesis [15]. Even by their changing the bone environment, they have been used as adjuvant treatment in order to prevent bone disease, although this issue remains controversial to date. In any case, they are a valuable addition to the therapeutic armamentarium, and oncologists of all disciplines will have to make themselves familiar with bone loss and its treatment.

References

1. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **365**: 60–62.
2. Thurlimann B, BIG 1–98 Collaborative Group. Letrozole versus tamoxifen as adjuvant andocrine therapy for postmenopausal women with receptor positive breast cancer. BIG 1–98: A prospective randomized double-blind phase III study. *The Breast* 2005; **14**(Suppl 1): S3 [Abstract S4].
3. Chlebowski RT, Col N, Winer EP, *et al*. American Society of Clinical Oncology Technology assessment of pharmacologic interventions for breast cancer including tamoxifen, raloxifen, and aromatase inhibition. *J Clin Oncol* 2002; **20**: 3328–3343.
4. Hillner B, Ingle J, Chlebowski R. 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.
5. Green JR, Muller K, Jaeggi KA. Preclinical pharmacology of CGP 42,446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res* 1994; **9**: 745–751.
6. Kanis JA, McCloskey EV, Powles T, *et al*. A high incidence of vertebral fracture in women with breast cancer. *Br J Cancer* 1999; **79**: 1179–1181.
7. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000; **18**: 1570–1593.
8. Brufsky A, Harker W, Beck R, *et al*. The Z-Fast Study Group. Zoledronic acid (ZA) effectively inhibits cancer treatment-induced bone loss (CTIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant Letrozole (Let): 12 months BMD results of the Z-FAST trial. *Proc ASCO* 2005; [Abstract 533].
9. Jakesz R, Hausmaninger H, Kubista E, *et al*. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – the Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002; **20**: 4621–4627.
10. Jordan VC, Fritz NF, Tormey DC. Endocrine effects of adjuvant chemotherapy and long-term tamoxifen administration on node-positive patients with breast cancer. *Cancer Res* 1987; **47**: 624–630.
11. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol* 2001; **19**: 3306–3311.
12. Gnant M, Jakesz R, Mlineritsch B, *et al*. The ABCSG. Austrian Breast & Colorectal Cancer Study Group. Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen – bone density subprotocol results of a randomized multicenter trial (ABCSG-12). *San Antonio Breast Cancer Symposium*, San Antonio, TX, USA, 2004.
13. Chang JT, Green L, Beitz J. Renal failure with the use of zoledronic acid. *New Engl J Med* 2003; **349**: 1676–1679.
14. Lanza FL. Gastrointestinal adverse effects of bisphosphonates: etiology, incidence and prevention. *Treat Endocrinol* 2002; **1**: 37–43.
15. Saba N, Khuri F. The role of bisphosphonates in the management of advanced cancer with a focus on non-small cell lung cancer: mechanisms of ation, role of biomerkers and preclinical applications. *Oncology* 2005; **68**(15): 92–94.

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