Osteoporosis and aromatase inhibitors: experience and future prospects

Daniela Bosco

UOSD of Endocrinology,
AO San Giovanni Addolorata, Rome, Italy

Address for correspondence:
Daniela Bosco, MD
UOSD of Endocrinology
AO San Giovanni Addolorata
Via Amba Aradam, 9
00185 Rome, Italy
Phone/Fax: +39 06 77055753
E-mail: daniela.bos17@gmail.com

Summary

Introduction. **The aim of this study is to improve the assistance given to patients under treatment with aromatase inhibitors in order to prevent secondary osteoporosis through the planning of an awareness programme for the oncologist and offering a facilitated treatment path.**
Materials and methods. **Thirty-nine postmenopausal women treated with aromatase inhibitors for breast cancer were selected. For each subject, the age at the beginning of the therapy, the type of aromatase inhibitors and the age at the performance of the bone densitometry was registered. In addition, the use of osteoporosis medication and supplementation of calcium and vitamin D were evaluated. Participants were required to answer a questionnaire consisting of closed questions relating to booking procedures of the bone densitometry and about their own knowledge of osteoporosis related to the use of aromatase inhibitors.**
Conclusions. **Although there is evidence of negative impact of the aromatase inhibitors on bone, our data still show a poor application of the recommendations in order to prevent osteoporosis related to the administration of these drugs.**
Our suggestion is a more active implementation of the guidelines, also by means of a greater collaboration between the oncologist and the specialist in osteoporosis, and the offer of a diagnostic and therapeutic pathway.

KEY WORDS: aromatase inhibitors; breast cancer; osteoporosis.

Introduction

Aromatase inhibitors of third generation (exemestane, anastrazole, letrozole) (AI) are now a standard of care for postmenopausal women with hormone receptor positive early stage and metastatic breast cancer (1-4). They have shown themselves to be superior to the previous tamoxifen in terms of the efficacy, safety and tolerability profile (5). One side-effect of these three compounds, however, is a decrease in bone mineral density (BMD) and an increased risk of fracture (6-10). In fact, by blocking the conversion of androgens to estrogens in peripheral tissue, they have proven to suppress plasma and tissue estrogen level by > 98% *in vivo*. On the other hand, it is well known that estrogens have a positive effect on bone metabolism by stimulating bone growth and inhibiting bone resorption, so their depletion in patients with endocrine-responsive breast cancer leads to increased bone demineralization and finally osteoporosis occurs.
In fact, various studies demonstrated that estrogens deprivation caused by AI intake has a negative effect on bone health. Bone mineral density rapidly decreases resulting in increased risk of skeletal fragility. For the prevention of this adverse event, antiresorptive agents such bisphosphonates are used in combination with AI (11-18). Recently, also denosumab, a human monoclonal antiboby anti RANK-L, is being investigated as an alternative treatment to bisphosphonates for the long-term management of bone loss in women with breast cancer (19,20).
Due to the association of AI and decreased BMD, practical guidelines have been developed for the management of these important side-effects (16). Firstly, it is well accepted that all postmenopausal women initiating therapy with AI should receive calcium and vitamin D supplements. Additional therapy with bisphosphonates should be considered for patients suffering from osteopenia to avoid the progression to osteoporosis. Osteoporosis at baseline should be treated as usual in accordance with the guidelines. The evaluation of BMD is recommended prior to initiation and at least every second year during treatment with AI.
In this study we investigated the management of bone health in postmenopausal women with breast cancer who were treated with AI considering it as an important component of long-term cancer care.

Materials and methods

Thirty-nine postmenopausal women who have been treated for breast cancer and have taken an AI were enrolled for the study. In all subjects we recorded: the age at the beginning AI therapy; the type of AI taken; their age upon measurement of BMD; the serum value of calcium and vitamin D and if they received any supplementation with calcium and vitamin D or/and any treatment with bisphosphonates. We required the participants to answer a questionnaire consisting of closed questions relating to booking procedures of the bone densitometry and about their own knowledge of osteoporosis related to the use of AI (Figure 1).

Results

Two subjects had measured BMD two years before the initiating therapy. Eight subjects had never measured BMD. Depending on when therapy was started, among the remaining twenty-nine women, six performed the mineral densitometry in the first year, ten in the second and third year, four in the fourth and fifth year and nine after the end of the therapy (Figure 2). Only eight subjects evaluated serum calcium and vitamin D during the therapy and they are still taking supplementation of calcium and vitamin D3. In regard to BMD measurements (in accordance with the World Health Organization definition) (21) fifteen patients are suffering from osteoporosis but only one patient has been taking bisphosphonates (Figure 3).

WHO RECOMMENDED THE BONE MINERAL DENSITOMETRY ?

Personal physician | *Personal initiative / recommended by friends* | *oncologist* | *other specialist*

HAVE YOU BEEN INFORMED OF THE EFFECTS ON THE BONE RELATED TO THE AROMATASE INHIBITORS?

yes | *no*

WHO BOOKED THE BONE MINERAL DENSITOMETRY?

Breast specialist | *oncologist* | *Personal initiative* | *others*

Figure 1 - Questionnaire relating to booking procedures of the bone mineral densitometry and about the women's knowledge of osteoporosis related to the use of aromatase inhibitors.

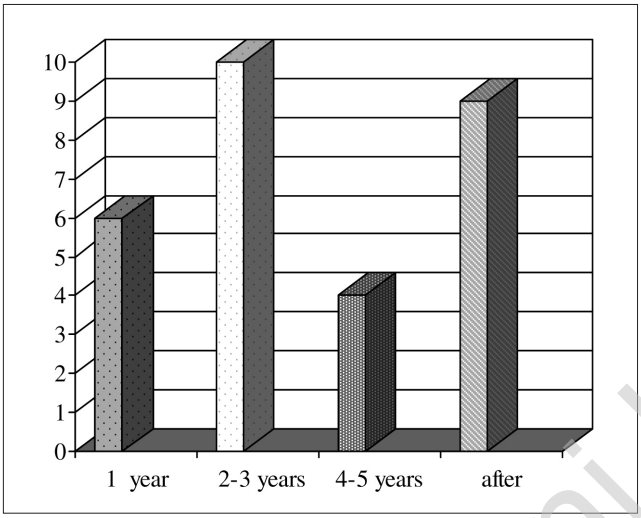

Figure 2 - Numbers of subjects who performed the bone mineral densitometry depending on when aromatase inhibitors were initiated.

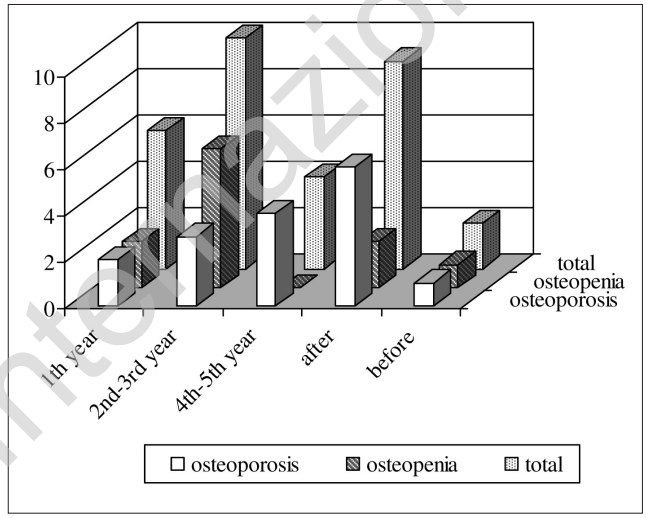

Figure 3 - Results of bone mineral densitometry in the subgroups of patients divided by the timing of the performance of the radiological exam.

The collection of questionnaire data shows that the BMD measurement was required by the oncologist only in 14% of the cases and mainly by the personal physician (Figure 4).
Only 31% of the subjects (12 women) is aware of the negative effect of AI on the bone (Figure 5).
Booking the radiological examination is entirely left to the patient.

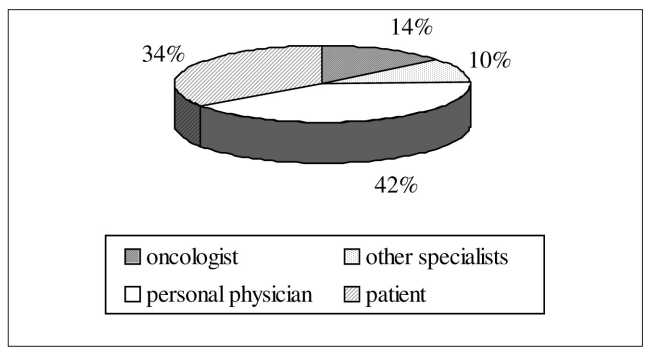

Figure 4 - Subjects who recommended the bone mineral densitometry.

Discussion

Breast cancer is the common cancer affecting women in Italy (17.1%) in accordance with the estimate from the *Associazione Italiana Registri Tumori* (AIRTUM) (22). The introduction of AI during the last decade has opened new horizons in the successful treatment of hormone receptor positive breast cancer. Their effectiveness is widely established in the adjuvant therapy of postmenopausal women with hormone responsive breast cancer in upfront, switch and sequential treatment settings. The use of the AI for the treatment of breast cancer has contributed to the survival of the patients but it accelerated bone loss related to estrogens deficiency.
Bone health is clearly an important concern in the management of these patients (23). The measurement of BMD at baseline has to be considered by oncologists as well as the clinical risk factors (history of fragility fracture in a first-degree relative, early menopause, low body mass index, smoking, excessive alcohol consumption). Specific guidelines on the evaluation and the management of the osteoporosis AI-correlated have already been outlined by important organizations such as National Osteoporosis Foundation, American Society of Clinical Oncology. However, our findings indicate that the focus on bone health by the physician who prescribes AI (the oncologist) is still poor. The decision to evaluate the BMD and the other parameters of bone metabolism is delegated to the personal physician/other specialists or to the personal initiative of the patient who responds to the effect of the media campaigns against osteoporosis.
On the other hand in our findings those individuals who are deemed to be at an increased risk of fracture do not receive adequate therapy and the whole group of patients do not take any calcium

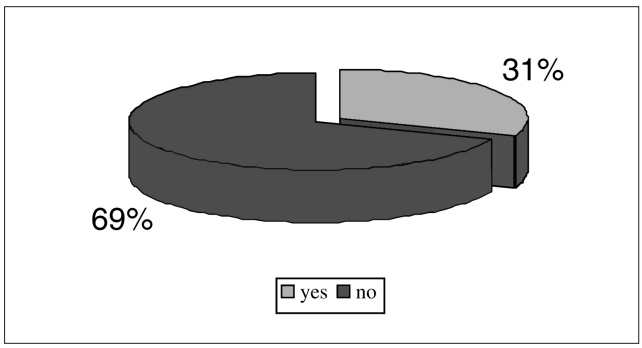

Figure 5 - Knowledge of the negative effect on bone health by the aromatase inhibitors.

and/or vitamin D supplementation.
Without effective intervention to prevent the diminishing skeletal health in postmenopausal women, the incidence of osteoporosis, and therefore, fractures, long-term dependence and mortality will increase resulting in a significant financial burden on the health care system. It is imperative that we identify preventive strategies rather than deal with the consequences of reduced BMD.
The oncologist is the physician who prescribes AI and follows the patient over time. Therefore, he plays a crucial role in the prevention of the side-effects of using the drug.
Our proposal is to set up training courses (conferences, seminars, meetings) on osteoporosis in which the oncologist is involved directly inside the hospital itself. Moreover, the multifactorial nature of osteoporosis explains the involvement of many different specialists and the collaboration amongst them ensures a more correct medical assistance. Another important objective is to create a facilitated care path, in which women are involved, providing the reservation of clinical tests (mineral bone densitometry, serum parameters of bone metabolism) and the timing of clinical assessments. The easy admission to a predetermined working model as well the management of osteoporosis in primary prevention can guarantee greater attendance in the program.
Critical issues in the management of osteoporosis related AI can be identified in the application of a uniform program of prevention and in the absence of a cut-off indicating the subject at increased risk. Scientific data show that the greater reduction of BMD appears within the first 24 months. The chance to act at this stage would allow us to avoid or minimize the significant changes observed in the different skeletal sides. The availability of effective drugs like bisphosphonates would justify a reassessment of the refundability of those drugs also in terms of prevention. Further studies should be carried out to evaluate effective public healthcare spending. We have to consider the costs of using bisphosphonates in prevention and the costs related to the assistance of women with severe osteoporosis which result in additional healthcare (hospitalization, physiotherapy, home assistance) and social (early retirement, loss of working hours by relatives attending the patients) costs.

References

1. NCCN National Comprehensive Cancer Network Inc.: Clinical Practice Guidelines in Oncology: Breast Cancer. Available at: http://www.nccn.com.
2. Burstein HJ, Prestrud AA. American Society of Clinical Oncology Clinical Practice Guideline: Update on Adjuvant Endocrine Therapy for Women with Hormone Receptor-Positive Breast Cancer. J Clin Onc. 2010 Aug; 28(23):3784-3796.
3. Aebi S, Davidson T, Gruber G, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21(Supplement 5):v9-v14.
4. Goldhirsch A, Wood WC, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007; 18(7):1133-1144.
5. Vestergaard P. Effect of Tamoxifen and Aromatase Inhibitors on the Risk of Fractures in Women with Breast Cancer. Calcif Tissue Int. 2008; 82:334-340.
6. Ghazi M, Roux C. Hormonal deprivation therapy-induced osteoporosis in postmenopausal women with breast cancer. Best Pract Res Clin Rheumatol. 2009 Dec; 23(6):805-11.
7. Jones S, Stokoe C, Sborov M, et al. The effect of tamoxifen or exemestane on bone mineral density during the first 2 years of adjuvant treatment of postmenopausal women with early breast cancer. Clin Breast Cancer. 2008 Dec; 8(6):527-32.
8. Geisler J, Lønning PE. Impact of aromatase inhibitors on bone health in breast cancer patients. [Journal of Steroid Biochemistry and Molecular Biology Web site]. Available at: http://www.elsevier.com.
9. 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 Feb; 119(3):643-51.
10. Folkestad L, Bjarnason NH, Bjerregaard JK, et al. The effect of aromatase inhibitors on bone metabolism. Basic Clin Pharmacol Toxicol. 2009 Jan; 104(1):3-10.
11. Hines SL, Mincey B, Dentchev T, et al. Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. Breast Cancer Res Treat. 2009 Oct; 117(3):603-9.
12. Bundred NJ, Campell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer. 2008; 112(5):1001-1010.
13. 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 May; 9(2):77-85.
14. Fricia T. et al. The adjuvant treatment with anastrazole in elderly women with early breast cancer: risk of bone fractures and protective role of risedronic acid. Gerontol. 2010; 58:31-36.
15. 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 Feb 20; 28(6):967-75.
16. 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(2):R24.
17. Greenspan SL, Brufsky A, Lembersky BC, et al. Risedronate Prevents Bone Loss in Breast Cancer Survivors. A 2-Year, Randomized, Double-bind, Placebo-Controlled Clinical trial. J Clin Oncol. 2008; 26 (16):2644-2652.
18. Adam Brufskya, Nigel Bundredb, Robert Colemanc, et al. Integrated Analysis of Zoledronic Acid for Prevention of Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole. Z-FAST and ZO-FAST Study Groupsh. The Oncologist. May 2008; 13(5):503-514.
19. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol. 2008; 26 (39): 4875-82.
20. Reid DM, Devogelaer JP, Saag K, et al. Trial of Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors for Nonmetastatic. Br Ann Oncol. 2008; 19:614-622.
21. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.
22. Associazione Italiana Registri Tumori (AIRTUM). Available at: http://www.registri-tumore.it.
23. Hadji P, Body JJ, Aapro MS, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol. 2008; 19 (8):1407-1416.