A Retrospective Study on Screening and Management of Osteoporosis in Breast Cancer Women Treated With Aromatase Inhibitors in Libya

H. Abushwereb[1,*], *M. Elhabash* [2], *S. Elhamshari*[1] *and H. Eshaefi* [1]

[1]Pharmacology and Clinical Pharmacy Department, University of Tripoli, Faculty of Pharmacy, Tripoli, Libya.
[2]Oncology Department, Tripoli Medical Center, Tripoli, Libya.

Abstract: Negative health effects of aromatase inhibitors (AI) treatments on bones such as osteoporosis are evidenced. This impact of the aromatase inhibitors on bone.This study aimed to improve the medical assistance given to patients under AI treatment to minimize secondary osteoporosis.Fifty Libyan postmenopausal women treated with AIto fight breast cancer were selected fromattendants Tripoli Medical Center (TMC), Oncology Department during year 2014. A closed questionnaire was requested from each women including data about age, age at AI therapy, and types of AI, age at bone densitometry measurement, onset and symptoms of osteoporosis,treatment of osteoporosis and measurement of vitamin Dand calcium supplement given. The study revealed a poor consideration given to apply the recommendation in cases suffering osteoporosis events.Ourresults suggest an active implementation of the guidelines concerning the high corporation levels that should be done between oncologist, specialist in osteoporosis, and patients to offer reliable diagnostic and post-therapyfollow up.

Keywords: aromatase inhibitors; breast cancer; osteoporosis.

1 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 (1118). Recently, also denosumab, a human monoclonal antibody 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, itis 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 treatedin TMC with AI considering it as an important component of long-term cancer care.

2 Subjects and Methods

Fifty postmenopausal women who have been treated for

* Corresponding author E-mail: *H.Abushwereb@uot.edu.ly*

breast cancer and have taken an AI (>1 year) were enrolled for the study. In all subjects, we recorded: the age at the beginning of AI therapy; the type of AI taken; their age upon measurement of BMD; the serum levels of calcium and vitamin D and if they received any supplementation with calcium and vitamin D or/and any treatment with bisphosphonates. We requested the participants to answer a questionnaire consisting of closed questionsrelating to booking procedures of the bone densitometry and about their own knowledge of osteoporosis related to the use of AI (Figure 1).

3 Results

Depending on when therapy was started,the fiftyof subjects involved in this studyhad never measured BMD before initiating the AI therapy. Concerningimportance of BMD measurements (in accordance with the World Health Organization definition) (21), All individuals subjected to questionnairedid not measure BMD duringthe course of their therapy. The collection of questionnaire data shows that amongall women, none of them performed the mineral densitometry neither in the first yearnor after the end of the therapy. The questionnaire data (Figure 2) also showed that the more incidence of breast cancer and its therapy were in younger Libyan women (58%) than in elder ones (38%). Twenty-seven women were treated with Letrozoletypeof AI followed by anastrazole and exemestane (Figure 3).Only eight (16%) subjects have been aware of the negative effects of AI on bone (Figure 4). They were evaluated serum calcium and vitamin D during the therapy and they are still taking supplementation of calcium and vitamin D3 (Figure 5). Thirty one patients (37%) are suffering from bone ache (onsetl of osteoporosis) (Figure 6). However, no patient has been diagnosed for osteoporosis or taking bisphosphonates.Only twelve women were aware about the importance of exercise and so doing exercise semi regularly in their life (Figure 7).
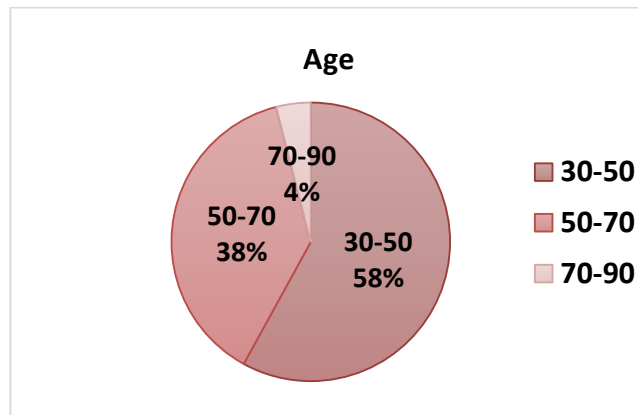
Have you been Informed of the effects on the bone related to the aromatase inhibitors?
Yes   no
Have you been asked or booked to perform Bone Mineral Densitometry?
Yes   no
IF yes who recommended the BMD?
OncologistBreast specialist other specialist
Have you been informed to take supplement (vitamin D or calcium)?
Yes   no
Are you normally doing exercise? As life style?
Yes   no
Are you a housewife or a worker?
Yes   no

Figure 1. Questionnaire relating to women's knowledge of osteoporosis related to the use of aromatase inhibitors.

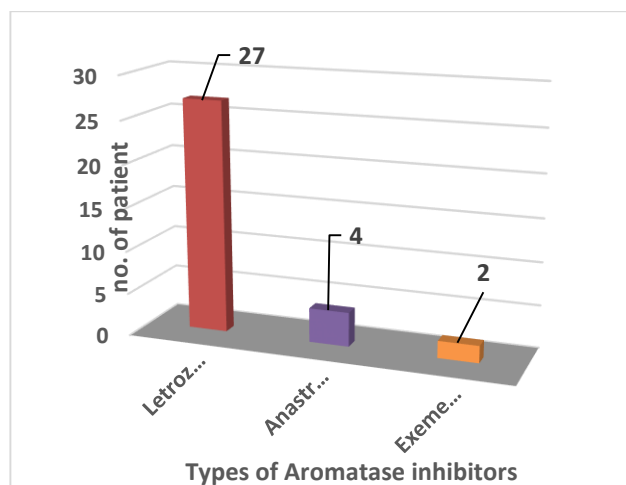**Figure 2.**Women's age at the beginning of AI therapy.

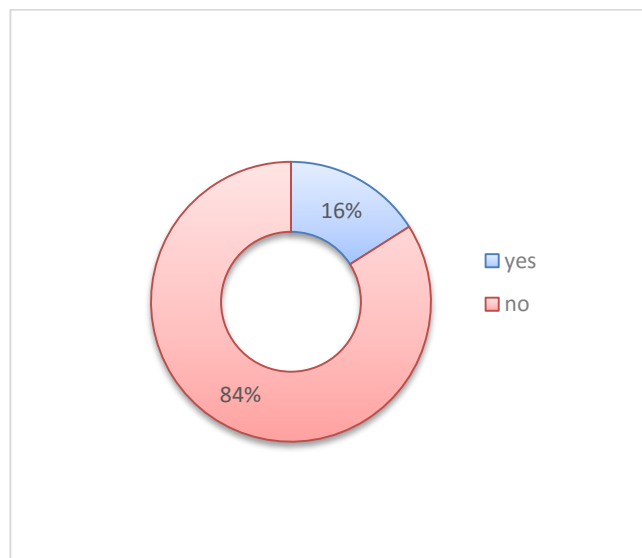**Figure 3.** Types of Aromatase inhibitors used in treatment of 50 breast cancer women in TMC 2014.

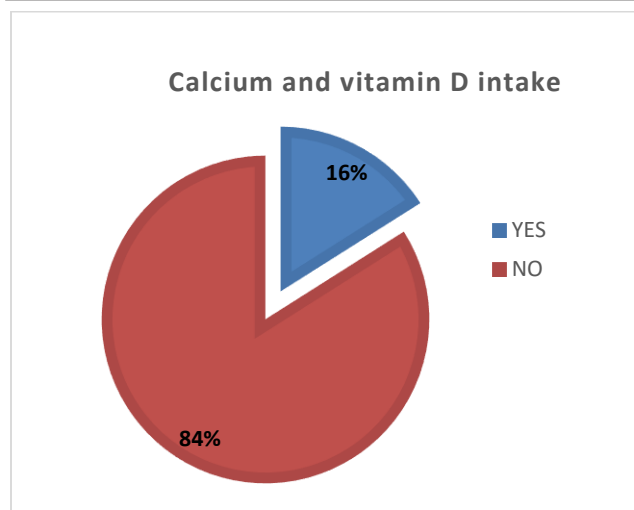**Figure 4.** Subjects awareness of the negative effect of AI on bone.

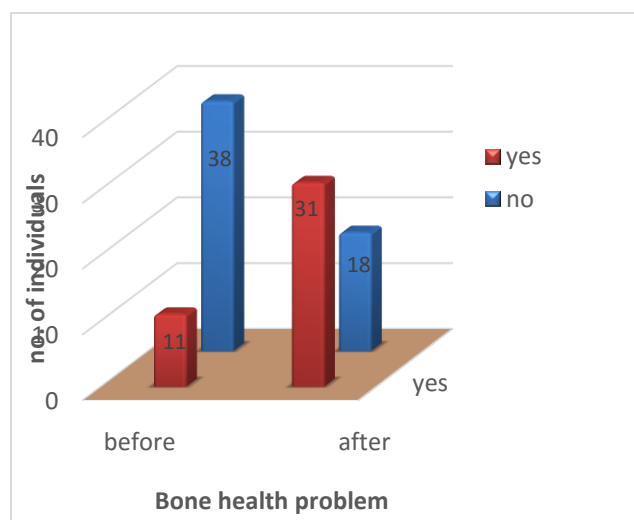**Figure 5.** Women taking calcium and vitamin D supplements.

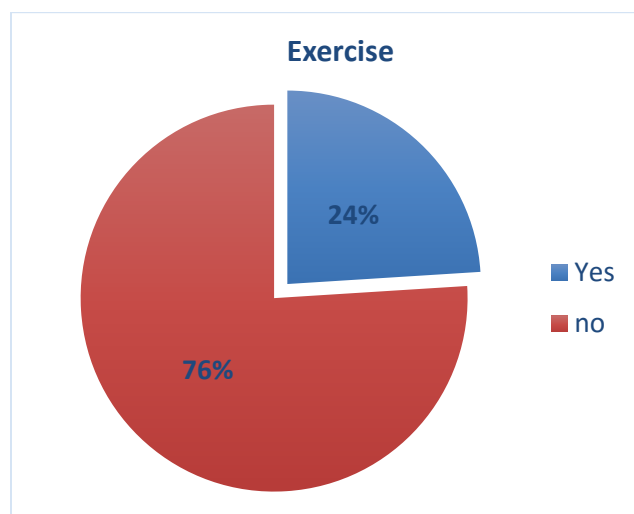**Figure 6.** Bone health problemof 50 breast cancer women before and after AI treatment in TMC 2014.

Figure 7: Women doing exercise.

4 Discussion

Breast cancer is now common in abundance among Libyan womenand in the world. Libyan hospitals and centers teeming with people living with this type of cancer.Unfortunately, there are still shortcomings in determining the precise numbers and stats to determine the extent of such problem in Libya.Theintroduction 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.Loss of bone consistency is a common side effect of long-term estrogen-reducing therapies.

Unfortunately, this important problem is not recognized as often as it should be.Thus, bone health is clearly an important concern in the management of these patients (22, 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 out-lined 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 andthe other parameters of bone metabolism is delegated to the personal physician/other specialists or to the personal initiative of the patient who positively 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 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 to 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 then is to aware about the need for the education of patients by a doctor, therapist and a doctor who will prescribe the treatment of tumors. Over and above, the necessity 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.

Critical issues in the management of osteoporosis related AI can be identified in the application of any 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 (24). The chance to act at this stage would allow the physician 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 refund ability of those drugs also in terms of prevention. There are some other simple but very important things women can do to help protect their bone health during and after cancer treatment time.Ensure that they have adequate calcium, vitamin D intake in addition to exercise. Healthy lifestyle habits are also important for keeping bones strong. Thus, the issue of education and awareness are still the main thing.

5 Conclusion

Further studies should be carried out to: (1) 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) costs.(2) establish efficient awareness programs for health care.

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 ClinOnc. 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 ClinRheumatol. 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 ClinPharmacolToxicol. 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 ClinOncol. 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 ClinOncol. 2008; 26 (16):2644-2652.

[18] Adam Brufskya, Nigel Bundredb, Robert Colemanc, et al. Integrated Analysis of Zoledronic Acid for Prevention of Aromatase InhibitorAssociated 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 ClinOncol. 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] 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.

[23] Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. J Natl ComprCancNetw 2013; 11 Suppl 3:S1.

[24] Daniela Bosco. Osteoporosis and aromatase inhibitors: experience and future prospects. 2012. Clinical Cases in Mineral and Bone Metabolism 2012; 9(2): 89-91.