A retrospective study on screening and management of osteoporosis in breast cancer women treated with aromatase inhibitors in Libya

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Summary
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 AI to fight breast cancer were selected from attendants Tripoli Medical Center (TMC), Oncology Department during year 2014. A closed questionnaire was requested from each woman 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 D and calcium supplement given. The study revealed a poor consideration given to apply the recommendation in cases suffering osteoporosis events. Our results suggest an active implementation of the guidelines concerning the high corporation levels should be done between oncologist, specialist in osteoporosis, and patients to offer reliable diagnostic and post-therapy follow up.

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 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, 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 in TMC with AI considering it as an important component of long-term cancer care.

Subjects and methods
Fifty postmenopausal women who have been treated for 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 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
Depending on when therapy was started, the fifty of subjects involved in this study had never measured BMD before initiating the AI therapy. Concerning importance of BMD measurements (in accordance with the World Health Organization definition) (21), all individuals subjected to questionnaire did not measure BMD during their AI therapy. Concerning importance of BMD measurements (in accordance with the World Health Organization definition) (21), all individuals subjected to questionnaire did not measure BMD during their AI therapy.
ring the course of their therapy. The collection of questionnaire data shows that among all women, none of them performed the mineral densitometry neither in the first year nor 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 letrozole type of AI followed by anastrozole 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).

Discussion

Breast cancer is now common in abundance among Libyan women and 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. 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. 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 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 per-

| 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? |
| Oncologist                     |
| Breast 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.
sonal 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.

In 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.
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