Approach in aromatase inhibitors - induced osteoporosis: results from an Italian multicenter observational study

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Summary

***Background*. Breast cancer (BC) is one of the most frequent cancer worldwide with about 25% of new cases in female population. Aromatase inhibitors (AIs) are recommended by National and International guidelines as treatment for women affected by BC estrogen receptor-positive tumors. However, these drugs, blocking the enzyme converting androgens into estrogens, might result in reduction of bone mineral density (BMD). Although since 2012 the use of anti-resorptive drugs was recommended for AIs-associated bone loss, only few patients received this treatment in real practice. Therefore, we aimed to assess the appropriateness of the management of AIs-associated bone loss by oncologists and bone specialists in BC women.**

***Methods*. In this Italian multicenter retrospective study, we included women affected by BC referred to 11 Italian Centers for Osteoporosis from two Italian regions (Lazio and Campania) in a 2 year-period (from March 2013 to February 2015). We evaluated the difference in terms of appropriateness of bone health management according to the 2012 European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), Position Paper between oncologists and bone specialists (endocrinologists, physiatrists, rheumatologists, internists, geriatrists, and gynecologists).**

***Results*. We included 300 women affected by BC, mean aged 63.26 ± 9.48 years, 182 (60.67%) treated with anastrozole, 87 (29.00%) with letrozole, and 31 (10.33%) with exemestane. Anti-osteoporotic drugs were prescribed in 87 patients (29.0%) by oncologists and in 216 patients (72.0%) by bone specialists. We found that only 44.67% were appropriately managed in terms of bone health by the oncologists, compared to 71.17% of cases by bone specialists.**

***Conclusions*. This Italian multicenter retrospective study showed a more appropriate management of AIs-induced osteoporosis by bone specialists, demonstrating a key role of these physicians in the bone health management of BC patients.**

KEY WORDS: aromatase inhibitors; osteoporosis; breast cancer; anti-osteoporotic treatment; oncology.

Introduction

Breast cancer (BC) is the most frequent malignant tumor in women in Europe and in North America, representing about

25% of new female cancer cases, with a predictive increasing incidence in the next years (1). The American Society of Clinical Oncology (ASCO) guidelines recommend the use of the aromatase inhibitors (AIs) in women affected by BC with estrogen receptor-positive tumors (2).
By blocking aromatase, the enzyme converting androgens into estrogens (3), AIs induce a reduction in bone mineral density (BMD) with a resulting increased risk of fragility fractures in women (4-6).
In 2003, ASCO recommended the screening for managing bone health in women with BC, including those receiving adjuvant endocrine therapy, in order to indicate an appropriate drug therapy to reduce the increased risk of fragility fractures. At that time the unique pharmacological approach was the use of bisphosphonates (BPs) (7).
Similar advices were recently highlighted and also proposed in subsequent practical guidance for the management of AIs-associated bone loss (8), and in a position paper by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (9), that confirmed the importance of the evaluation of the bone health in women treated with AIs, in order to start an anti-resorptive treatment with oral BPs, zoledronic acid or denosumab. In Italy, only in May 2015, it was established, by the Italian reimbursement criteria for anti-osteoporotic pharmacological treatment, that women aged ≥50 years affected by BC, in treatment with AIs, should be treated by alendronate, risedronate, zoledronate or denosumab (10).
Although the unanimous agreement, these recommendations were not followed by all physicians who take care of patients with BC, likely due to underestimation and consequent inadequate management of the potential negative effects of AIs on skeletal metabolism.
Therefore, the aim of this multicenter Italian retrospective study was to evaluate the appropriateness of the management of AIs-associated bone loss by bone specialists and by oncologists, according to the ESCEO position paper, in a cohort of women affected by BC.

Methods

The study respects the Declaration of Helsinki and was approved by the local Ethical Committees of the institutions involved. All the participants were asked to carefully read and sign an informed consent, taking precautions to protect the privacy of patients.
In this multicenter retrospective study, we included data records of women affected by BC referred to 11 different specialized Centers for Osteoporosis from two Italian regions (Lazio and Campania) of Center and South of Italy in a 2 year-period (from March 2013 to February 2015).
Inclusion criteria were: a) estrogen receptor positive (ER +) BC; b) treatment with AIs (anastrozole, letrozole, exemestane); c) presence of dual X-ray absorptiometry measurement at lumbar spine (LS) and femoral neck (FN) for BMD evaluation; d) previous bone assessment by an oncologist (until 1 year before the bone specialist assessment).
We evaluated the following data: age, body mass index (BMI), type of AIs therapy administered, menopausal age (if present), previous fragility fractures, history of fragility fracture in relatives, history of glucocorticoids use for over 3 months, current smoking, use of 3 or more units/day of alcohol, diagnosis of rheumatoid arthritis, FRAX 10-year major osteoporotic fracture probability and FRAX 10-year hip fracture probability.
Each patient was evaluated two times: the first time by an oncologist, the second time by a bone specialist, a physician expert in the management of bone diseases (i.e. endocrinologist, physiatrist, rheumatologist, internist, geriatrist, and gynecologist). At the end of both examinations, each physician decided to prescribe or not any anti-osteoporotic treatment.
We evaluated the appropriateness of bone health management according to the 2012 ESCEO position paper (9) that recommended an anti-resorptive treatment in: a) osteoporotic patients; b) patients older than 75 years; c) patients with at least one fragility fracture; d) patients with a LS or FN T-score <-1.5 SD, presenting at least one clinical risk factor (including age, parental fracture history, BMI <20 kg/m², corticosteroids use, cigarette smoking, inadequate nutritional intakes, disuse, tendency to falls, and conditions associated to osteoporosis); e) patients with a T-score <-1 SD and >-1.5, presenting at least two clinical risk factors; f) patients with a 10-year hip fracture FRAX risk ≥3%.

Results

The study includes 300 women with breast cancer, mean aged 63.26 ± 9.48 years with mean BMI 25.34 ± 3.87 kg/m^2. Each woman was in treatment with AIs, in particular 182 (60.67%) with anastrozole, 87 (29.00%) with letrozole, 31 (10.33%) with exemestane (Table 1). One-hundred-one patients (33.67%) experienced at least one previous fragility fracture: 62 vertebral fractures (61.39%), 18 wrist fractures (17.82%), 8 hip fractures (7.92%), 5 rib fractures (4.95%), 1 humeral fracture (0.99%), 1 ankle fracture (0.99%), 1 other fractures (0.99%), and 5 with multiple fractures (4.95%) (see Table 2 for further details).
Oncologists prescribed anti-osteoporotic drugs to 87 patients (29.0%); on the other hand bone specialists prescribed anti-osteoporotic drugs to 216 patients (72.0%).
According to the 2012 ESCEO position paper (9), only the 44.67% of women were appropriately managed by the oncologists, in terms of bone health, and in the 71.17% of cases by the bone specialists. In particular, of the 237 (79.00%) that should have received a prescription of anti-osteoporotic drugs, only 79 (26.33%) were treated by the oncologists and 184 (61.33%) were treated by the bone specialists. Moreover, it is interesting to notice that the oncologists prescribed an anti-osteoporotic treatment for 8 women (2.67%) that should not have been treated and the bone specialist treated 32 women (10.67%) that should not have been treated, according to the 2012 ESCEO position paper (9) (see Figure 1 for more details).
Among the 87 women with anti-osteoporotic prescription by the oncologists, 64 received oral BPs (73.6%), 11 strontium ranelate (12.6%), 8 clodronate (9.2%), 3 zoledronate (3.4%), and 1 neridronate (1.1%). Among the 216 women treated by the bone specialists, 139 received oral BPs (65.3%), 38 denosumab (17.8%), 21 zoledronate (9.9%), 10 neridronate (4.7%), 6 strontium ranelate (2.8%), and 2 clodronate (0.9%) (see Figure 2 for more details).

Discussion

This multicenter retrospective study aimed to assess the appropriateness of management of bone health by oncologists

Table 1 - Study population characteristics (n=300).

Mean age (years)	63.26 ± 9.48
BMI (kg/m^2)	25.34 ± 3.87
Menopause (n, %)	266 (88.67)
Menopausal age (years)	49.12 ± 3.83
Smokers (n, %)	76 (25.33)
Alcohol ≥3 units/day (n, %)	5 (1.67)
Glucocorticoids (n, %)	29 (9.67)
Surgery (n, %)	292 (97.33)
Chemotherapy (n, %)	169 (56.33)
Radiotherapy (n, %)	208 (69.33)
Family history for osteoporotic fracture (n, %)	114 (38.00)
Rheumatoid arthritis (n, %)	5 (1.67)
Aromatase inhibitors (n, %)	300 (100)
anastrozole	182 (60.67)
letrozole	87 (29.00)
exemestane	31 (10.33)

Continuous variables are expressed as means ± standard deviations, categorical variables are expressed as counts (percentages). Abbreviation: BMI= Body Mass Index.

Table 2 - Previous fractures, densitometric data and 10-year fracture probability assessed by FRAX (n=300).

Previous fracture (n, %)	101 (33.67)
vertebral	62 (61.39)
wrist	18 (17.82)
hip	8 (7.92)
ribs	5 (4.95)
ankle	1 (0.99)
humeral	1 (0.99)
other skeletal sites	1 (0.99)
multiple fractures	5 (4.95)
FN BMD (g/cm^2)	0.779 ± 0.166
FN T-score (SD)	-1.98 ± 1.00
FN Z-score (SD)	-0.61 ± 1.14
LS BMD (g/cm^2)	0.766 ± 0.131
LS T-score (SD)	1.95 ± 1.00
LS Z-score (SD)	-0.57 ± 1.07
FRAX 10-year major osteoporotic fracture probability (%)	12.80 ± 11.86
FRAX 10-year hip fracture probability (%)	5.52 ± 9.88

Continuous variables are expressed as means ± standard deviations. Abbreviations: BMD= Bone Mineral Density, FN= Femoral Neck, LS= Lumbar Spine.

and bone specialists in a cohort of patients affected by BC. Data were collected for a 2-year period from March 2013 to February 2015, before the introduction of patients treated with AIs in the Italian reimbursement criteria for anti-osteoporotic pharmacological treatment in 2015 (10) and subsequently in 2017 (11). Therefore, according to the 2012 ES-

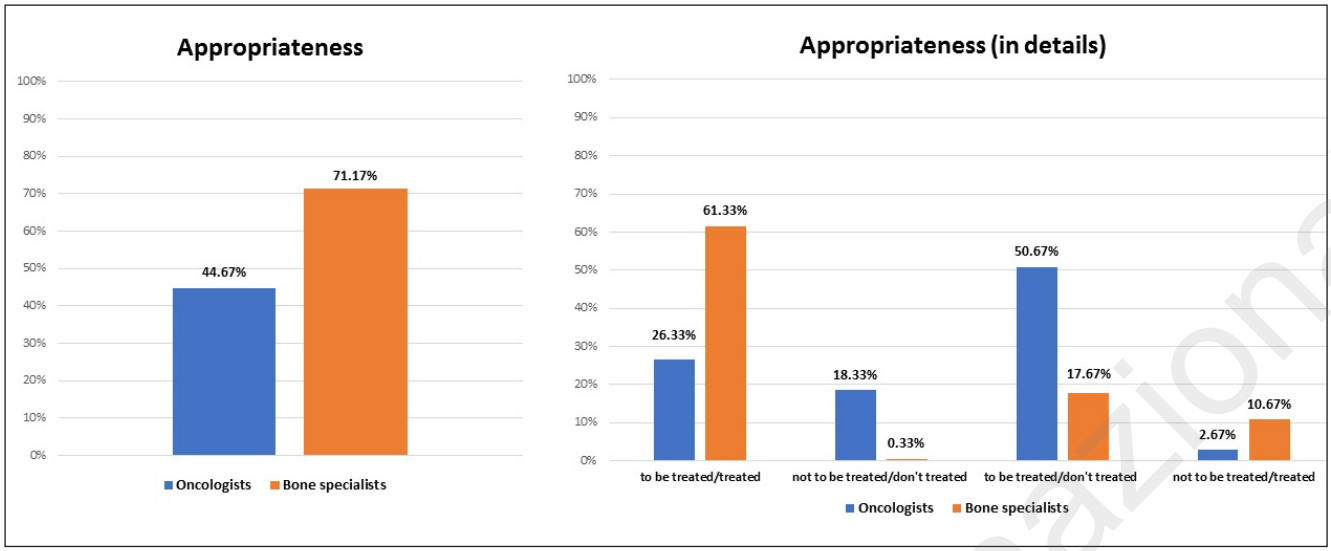

Figure 1 - Appropriateness of oncologist and bone specialist management of the bone health (n=300).

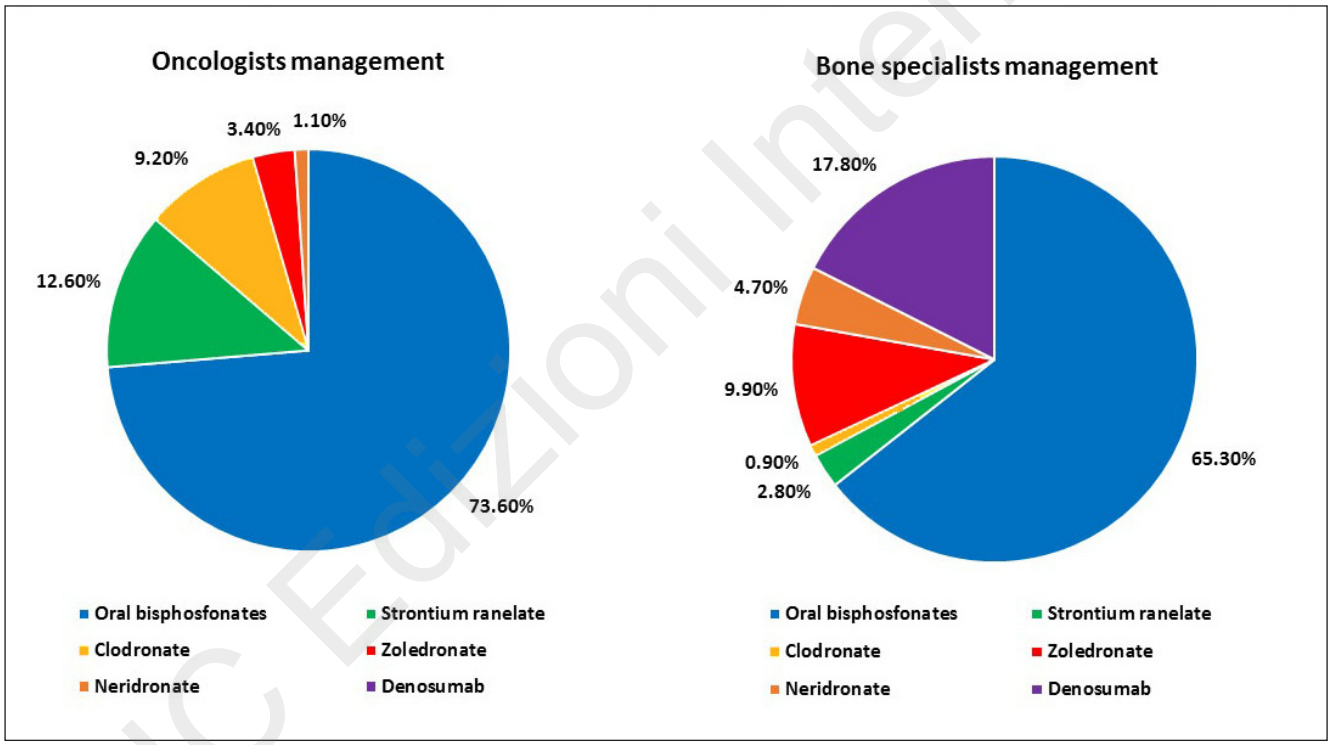

Figure 2 - Anti-osteoporotic treatment prescribed by oncologist (n=87) and bone specialist (n=216).

CEO position paper (9), the 71.17% of cases were appropriately managed by the bone specialists and only the 44.67% by the oncologists. These data showed that more than 50% of women that should have been treated did not receive any prescription of anti-osteoporotic drugs by the oncologists, despite the ESCEO recommendation (9). Moreover, of the 237 women that should have been treated, the bone specialists prescribed anti-osteoporotic drugs in 61.33% patients, whereas only the 26.33% was treated by the oncologists.

The ASCO clinical practice guidelines, firstly in 2000 (12) and successively updated in 2003 (7), recommended the BMD assessment, advising lifestyle modification, calcium and vitamin D supplementation, and anti-osteoporotic therapy (based on T-score) in women with BC in AIs therapy. Even the ESCEO considered mandatory the bone health evaluation in women treated with AIs, in order to start an adequate anti-osteoporotic therapy.

The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) study demonstrated that anastrozole reduced LS and total hip BMD after 1 year (-2.26% and -1.51%, respectively), after 2 years (-3.97% and -3.92%) (13), and after 5 years (-6.08% and -7.24%) (14) in women affected by BC. Moreover, the Authors showed an increase in LS and total hip BMD both at 1 year (+2.35% and +0.71%, respectively) and at 2 years (+4.02% and +0.50%), after the completion of 5-year adjuvant treatment (4).

The Breast International Group (BIG) 1-98 study, a randomized, phase 3, double-blind trial, showed that letrozole leads to a high prevalence of densitometric osteoporosis after 3 years (15.4% at LS *vs* 8.6% at hip); on the other hand, at 1 year after the end of the 5-year treatment the prevalence of densitometric osteoporosis was severely reduced (1.6% at LS vs 2.9% at hip) (15).

The Mammary Prevention 3 (MAP.3) trial showed that exemestane reduced LS BMD (-2.4%), total hip (-1.8%), and FN BMD (-2.4%) after 2 years in post-menopausal women with BC (16).

Therefore, as showed by literature, the AIs therapy has a considerable negative effect on bone health, making necessary an appropriate and prompt prescription of anti-osteoporotic drugs.

Several studies demonstrated the efficacy of the use of BPs in maintaining skeletal health in patients treated with AIs (17-19).

The adjuvant denosumab in breast cancer (ABCSG-18) trial, a recent study performed on post-menopausal women with BC in treatment with AIs, showed that denosumab significantly reduces the risk of clinical fractures in terms of delayed time to first clinical fracture (20).

As proof of the importance of this finding, in 2015, patients in treatment with AIs were included in the Italian reimbursement criteria for anti-osteoporotic pharmacological treatment (10), subsequently updated in 2017 (11), to be prescribed alendronate (with or without vitamin D), risedronate, zoledronate, and denosumab as first choice-options.

Furthermore, the Italian Association of Medical Oncology (AIOM, *Associazione Italiana di Oncologia Medica*) highly recommends the use of denosumab and BPs during the entire period of AIs therapy for prevention or treatment of osteoporosis.

Despite extensive scientific literature and supporting international guidelines, oncologists, in the historical period examined in the study, did not have a correct perception of the importance of the problem.

As we would expect, there was better knowledge by bone specialists of the consequences of AIs therapy on bone health. Moreover, the bone specialists used a broader spectrum of anti-osteoporotic drugs, where, in addition to other treatments, they prescribed denosumab, a novel human monoclonal antibody that inhibits osteoclastic-medicated bone resorption binding RANKL.

The main limitation of our study was that only two regions (Lazio and Campania) were involved, not making our data representative of the entire Italy. Moreover, another limitation is the lack of detailed data on bone metabolism biochemical exams.

To the best of our knowledge, this is the first study investigating the appropriateness of anti-osteoporotic prescription both in oncologists and in bone specialists according to the 2012 ESCEO position paper (9).

Conclusions

In this Italian multicenter retrospective study performed before the publication of the 2015 Italian reimbursement criteria for anti-osteoporotic pharmacological treatment, we showed a not appropriate management of AIs-induced osteoporosis in the entire cohort. On the other hand, our findings showed better prescription appropriateness by the bone specialists that should have a key role in the bone health management of BC patients.

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