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Early Denosumab for the prevention of osteoporotic fractures in breast cancer women undergoing aromatase inhibitors: A case-control retrospective study

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Abstract.
BACKGROUND: Aromatase inhibitors (AIs) might have a detrimental impact on bone health in breast cancer (BC) women. Denosumab has been shown to reduce the risk of fractures, but the appropriate time for starting is yet to be clearly defined.
OBJECTIVE: To evaluate the effects of early treatment with Denosumab ($\leqslant$ 12 months after starting AIs) compared to a delayed treatment in BC women.
METHODS: In this retrospective case-control study, we included medical records of BC post-menopausal women, treated with AIs therapy; they were divided as: study group (starting Denosumab $\leqslant$ 12 months after AIs) and control group ($>$ 12 months). At the baseline (T0) and at 18 months (T1), we evaluated the lumbar spine (LS) Tscore and femoral neck (FN) Tscore. Furthermore, at T1 we assessed the incident fragility fractures.
RESULTS: Fifty-nine BC survivors (mean age: 61.5 $\pm$ 11.5 years) were included: 28 with Early Denosumab and 31 with Late Denosumab. At T1, the study group did not show any incident hip or vertebral fragility fracture, whereas the Late Denosumab group showed 2 incident hip fractures (6.5%) and 4 (12.9%) vertebral fragility fractures. Early Denosumab showed a significant positive effect on both LS ($p = 0.044$) and FN ($p = 0.024$) Tscore variations.
CONCLUSION: Taken together, our findings suggest that an early start of Denosumab might be considered for the osteoporosis management in BC women undergoing AIs.

Keywords: Osteoporosis, risk of fractures, breast cancer, denosumab, bone health

1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women, accounting for 30% of female cancers, and the first cause of cancer death in women, followed by colorectum cancer [1,2]. The disease course

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has been changed in recent years with a great improvement of the 5-years survival estimated about 90% worldwide [2], and 87% in Italy [3].

BC management might consist of several therapeutic strategies, including surgery (mastectomy and quadrantectomy), often followed by local radiotherapy and chemotherapy, guided by tumor histology subtype. These interventions might lead to several disabling complications, including breast cancer-related lymphedema, BC-related fatigue, shoulder dysfunction, postural imbalance, axillary web syndrome, physiological disorders [4–6].

Breast surgery might lead to a significant physical and psychological impact in post-menopausal women, suffering range of motion limitation, pain and discomfort, a patient-tailored rehabilitation intervention is mandatory to prevent or resolve these complications. In the literature, several studies have shown that, regardless of surgery received, a low-intensity rehabilitation program is effective in recovering upper limb mobility and reducing disability and pain [7,8].

Adjuvant hormonal treatment is indicated in all patients with breast cancer with hormone receptor positive (ER+) after surgery to prevent disease recurrence [9,10]. Hormone Replacement Therapy (HRT) can be individualized based on the clinical evaluation, as various drugs can be administrated, such as estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and luteinizing hormone-releasing hormone (LHRH) agonists [9]. Among the SERMs, the most used in common practice is tamoxifen, in association or not with LHRH analogues, which is indicated in the treatment of pre-menopausal women with hormone receptor positive breast cancer [11]. On the other hand, AIs are utilized in post-menopausal women with ER+ [12].

In this scenario, AIs are considered as powerful inhibitors of estrogen production, acting by binding reversibly (non-steroidal inhibitors), or irreversibly (steroidal inhibitors) and deactivating the aromatase enzyme, responsible for the conversion of androgens into estrogens [13]. However, these therapies could have a detrimental impact on bone health in BC women, promoting bone resorption [14,15]. Indeed, the low circulating estrogen levels could lead to a high differentiation of the pre-osteoclasts, an increase in the survival of osteoclasts and an increased apoptosis of osteoblasts [14]. As a result, the osteoclasts activity will be greater than the activity of osteoblasts, with a negative effect on bone remodeling, leading to a cancer treatment-induced bone loss (CTIBL), during AIs administration or after the end of treatment [14–16]. Therefore, AIs assumption represents a noteworthy risk factor for the development of osteoporosis in BC survivors, as their prolonged use inevitably leads to a reduction in bone mineral density (BMD) [17] and an increased risk of fragility hip and vertebral fractures [18].

In this context, CTIBL is considered an emerging issue in BC survivors [19], and the Italian National Regulatory Agency for Drugs included BC women aged $\geqslant 50$ years treated with AIs in the subjects respecting the reimbursement criteria for anti-osteoporotic pharmacological treatments [20], thus recommending bisphosphonates (alendronate, risedronate, zoledronate) or Denosumab as a first-line approach [20].

Denosumab is a fully human IgG2 monoclonal antibody that binds and inhibit the receptor activator of nuclear factor kappa-B ligand (RANKL), a key mediator for bone resorption, with high affinity and high specificity. RANKL signaling cascade normally intervenes in promoting the survival of osteoclasts [21]. Denosumab assumption reduces bone resorption at both cortical and trabecular level [14]. Moreover, it has been shown that Denosumab 60 mg subcutaneously administered every 6 months in combination with vitamin D supplementation might reduce the risk of fragility fractures in BC survivors [14]. In addition to its antiresorptive effect, Denosumab also plays a role in improving BC survival, mainly by reducing the development of bone metastases [22], and reducing back pain-related disability [23,24]. Furthermore, patients undergoing Denosumab showed high persistence and adherence that might lead to a high therapeutic effect on bone health, reducing the risk of fragility fractures [25].

Although the effectiveness of Denosumab in reducing bone loss in BC women undergoing AIs is well recognized [11,13,15,18,22], the appropriate time for intervention is yet to be clearly defined. Some studies [14,15,18] showed the effectiveness of Denosumab in preventing fragility fractures and BMD loss at the start of HRT therapy; these findings have been confirmed by a recent metanalysis [26] in post-menopausal women undergoing AIs. On the other hand, evidence also showed that the effectiveness of Denosumab on BMD might still be preserved even if started after adjuvant therapy [15,27,28]. Therefore, in the present study, we sought to evaluate the effects of an early treatment with Denosumab ($\leqslant 12$ months after starting AIs) compared to a delayed treatment in BC post-menopausal women.

2. Materials and methods

2.1. Participants

In this retrospective case-control study, we included medical records of BC survivors referring to the Osteoporosis Outpatient Service, "Paolo Giaccone University Hospital", Palermo, Italy over a 24-month period, from January 2017 to January 2019. Inclusion criteria were: 1) post-menopausal women aged > 50 years; 2) diagnosis of histologically confirmed non-metastatic BC; 3) AIs therapy; 4) absence of prevalent osteoporotic fractures; 5) use of Denosumab 60 mg subcutaneously each 6 months as anti-osteoporosis treatment. We excluded: 1) women that previously assumed anti-osteoporosis drugs; 2) women in treatment with others anti-neoplastic therapy; 3) women with metastases.

The study was approved by the Ethics Committee of the "Paolo Giaccone University Hospital" in Palermo, Italy (approval number: 06/2019). Researchers provided to protect the privacy and the study procedures according to the Declaration of Helsinki, with pertinent National and International regulatory requirements.

2.2. Intervention

All study participants underwent Denosumab 60 mg by subcutaneous injection every 6 months, combined with an oral supplementation of cholecalciferol 25,000 IU (once every 15 days) and calcium citrate 500 mg (once per day).

The study cohort was divided according to the timing of the start of Denosumab treatment: study group, starting Denosumab no more than 12 months after the first AIs administration, and control group, starting Denosumab more than 12 months after the first AIs administration.

2.3. Outcome measures

At the baseline (T0) and at the 18-month follow-up evaluation (T1), we collected the following data: lumbar spine (LS) bone mineral density (BMD), LS Tscore, LS Zscore, femoral neck (FN) BMD, FN Tscore, FN Zscore, serum levels of 25-hydroxyvitamin D [25(OH)vit.D], calcium, parathyroid hormone (PTH), and alkaline phosphatase (ALP). Furthermore, at T1 we assessed the number of incident hip and vertebral fragility fractures.

2.4. Statistical analysis

The statistical analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as means and standard deviations, whereas the categorical variables were expressed as absolute numbers and percentages. For the statistical modeling we used the classical linear regression model to evaluate the effect net of any confounding variables. P-values < 0.05 were considered statistically significant.

3. Results

Of the 255 subjects recruited, 196 did not match the eligibility criteria and were excluded. Thus, 59 BC post-menopausal women (mean age: 61.5 ± 11.5 years) were included in the final analysis. The study cohort was divided into two groups based on the start of Denosumab treatment: the study group (Early Denosumab) included 28 patients, while the control group (Late Denosumab) included 31 patients. No statistically significant differences were found between the two groups at baseline for the collected outcomes, as shown in Table 1.

At T1, the study group did not show any incident hip or vertebral fragility fracture. On the other hand, it was interesting to notice that the Late Denosumab group showed 2 (6.5%) incident hip fractures and 4 (12.9%) incident vertebral fragility fractures. At T1, the study group showed higher BMD values compared to control, both for LS (0.79 ± 0.1 g/cm^3 vs 0.74 ± 0.2 gr/cm^3) and FN (0.88 ± 0.1 g/cm^3 vs 0.80 ± 0.3 g/cm^3), and consequently higher T-scores (LS -1.75 ± 1.3 vs -1.97 ± 1.1 and FN -1.25 ± 1.7 vs -1.51 ± 1.1).

We also performed a linear regression model considering the T-score at T0 to assess any difference between groups depending on the baseline status of the patient. Table 2 shows the estimates of the regression coefficients of the model for the variation of the LS T-score and the FN T-score. Considering the results of the main effects, an early administration of Denosumab 60 mg within one year from AIs therapy initiation showed a statistically significant positive effect on the variation of the T-score in both LS Tscore ($+0.169$; $p = 0.044$) and FN Tscore ($+0.234$; $p = 0.024$)

4. Discussion

AIs are considered to be the most administered hormonal therapies in post-menopausal women with BC. However, their assumption is detrimental for bone health in these patients, as they might cause reduction

Table 1
Baseline characteristics of the study population

	Total ($n = 59$)	Study group ($n = 28$)	Control group ($n = 31$)	P value
Age (years)	61.5 ± 11.5	62.6 ± 11.9	60.4 ± 11.2	0.486
BMI (kg/m^2)	26.4/6.3	26.4/6	26.5/6.7	0.987
Laterality (right/left/bilateral)	26/27/6	12/13/3	14/14/3	0.958
Type of breast cancer (lobular/ductal)	16/43	8/20	8/23	0.877
Histological type (in situ/infiltrative)	3/56	2/26	1/30	0.441
Previous femur fragility fractures	1 (1.69%)	1 (3.57%)	0 (0%)	0.972
Previous vertebral fragility fractures	47 (79.66%)	20 (71.4%)	27 (87.1%)	0.142
LS BMD (g/cm^2)	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.2	0.754
LS Tscore	−2.1 ± 1.2	−2.1 ± 1.2	−2.2 ± 1.3	0.732
LS Zscore	−0.6 ± 1.2	−0.6 ± 1.3	−0.7 ± 1.1	0.745
FN BMD (g/cm^2)	0.7 ± 0.3	0.7 ± 0.4	0.8 ± 0.2	0.591
FN Tscore	−1.5 ± 1.1	−1.4 ± 1	−1.5 ± 1.2	0.665
FN Zscore	−0.5 ± 1.3	−0.5 ± 1.4	−0.5 ± 1.1	0.963
Serum 25(OH)vit. D (ng/ml)	30.1 ± 15.8	27 ± 13.2	32.9 ± 17.6	0.153
Serum calcium (mg/dl)	9.1 ± 1.4	9 ± 1.5	9.2 ± 1.2	0.517
Serum PTH (pg/ml)	52.4 ± 23.6	52.6 ± 25.3	52.3 ± 22.4	0.965
Serum ALP (ug/l)	12.5 ± 11.1	10.8 ± 7.4	14 ± 13.7	0.270

Continuous variables are expressed as means ± standard deviations; categorical variables are expressed as counts (percentages); ratios are expressed as x/y. Abbreviations: BMI = body mass index; LS = lumbar spine; BMD = bone mineral density; FN = femoral neck; 25(OH)vit. D = 25-hydroxy-vitamin D; PTH = parathyroid hormone; ALP = alkaline phosphatase.

Table 2
Regression model for the variation of lumbar and femoral T-score from baseline (T0) to the 18-month follow-up evaluation (T1)

Coefficients	Estimate	Std. error	P value
Lumbar spine T-score at T1			
Lumbar spine T-score in T_0	−0.202	0.062	0.002
Early Denosumab	0.485	0.212	0.027
Age	−0.004	0.005	0.372
Lumbar T-score in T_0*Early Denosumab	0.169	0.086	0.024
Femoral neck T-score at T1			
Femoral T-score in T_0	−0.209	0.086	0.018
Early Denosumab	0.526	0.245	0.036
Age	−0.006	0.007	0.328
Femoral neck T-score in T_0*Early Denosumab	0.234	0.132	0.044

of BMD, with consequently hip and vertebral fragility fractures [17,18].

In the present retrospective case-control study, we assessed the effects of Denosumab 60 mg sc. every 6 months in women with non-metastatic BC on AIs therapy started no more than 12 months after the first AIs administration compared with the same therapy initiated more than 12 months after the first AIs administration. We showed that an early treatment with Denosumab might have a preventive effect on incident vertebral and hip fragility fractures, and a greater improvement in FN and LS T-scores compared to a delayed treatment. We also documented greater improvements in patients with previously deteriorated bone.

In the literature, several studies have shown the effectiveness of Denosumab in preventing negative effects on bone mineral metabolism in patients affected by BC under AIs treatment. Firstly, Ellis et al. [15] analyzed the efficacy of Denosumab versus a placebo in preventing bone health in women treated with AIs. The results of the study confirmed the efficacy of Denosumab compared to placebo in increasing BMD levels in the trabecular and cortical bone; however, the time of administration was not evaluated, as they only stratified patients by duration of AIs therapy (six months or more) stating no significant differences [15].

The phase III Adjuvant Denosumab in postmenopausal patients with hormone receptor-positive Breast Cancer (ABCSG-18) trial showed that Denosumab treatment resulted in increased lumbar and femoral neck BMD compared to placebo, as well as delaying onset of clinical fragility fracture [18]. However, the authors reported that 16% of the patients were enrolled at start of AIs therapy, whereas 84% of the patients were already under treatment; no clear assessment between the adequate time to initiate Denosumab was stated.

A recent meta-analysis [26] compared Denosumab versus zoledronic acid to prevent AI-associated fractures in postmenopausal early BC, showing that Denosumab started within 12 months from AIs might reduce the risk of fracture significantly compared with delayed treatment. However, the latter was performed only on two studies versus placebo and considering a subset of patients that crossed over due to deterioration of bone. Moreover, immediate vs late administration was comparable at the 18 month cut-off, while the risk of fracture was reduced only at 36 months. On the other hand, Nakatsukasa et al. [28] evaluated the efficacy of Denosumab in the treatment of AIs-associated bone loss in a Japanese population, assessing a similar increase in LS BMD in patients who received AI and Denosumab simultaneously and in patients who had received AI before the initiation of the Denosumab therapy, with no significant difference.

In the present study we found that BC women undergoing AIs starting the treatment with Denosumab within 12 months from AIs therapy might beneficiate in terms of fragility fracture prevention at 18 months follow-up compared to the same therapy performed after 12 months. Moreover, the early treatment with Denosumab seems to lead to a further increase of LS and FN T-scores compared to delayed treatment, and these effects might be greater in patients with reduced BMD. Indeed, it is crucial to define the better timing for starting antiresorptive agents to prevent fragility fractures in BC women undergoing AIs therapy. This study might be a step towards the better clinical management of these fragile patients.

As bone metabolism is still a growing field of knowledge, several mechanisms might contribute to CTIBL, such as inflammation, hematological alterations, and different hormonal disbalance [29,30].

However, it should be stressed that aside from pharmacological treatments, an adequate physical activity might play an important role in the prevention of bone loss in BC patients [31].

We are aware that the present study is not free from limitations: first, the monocentric study design might not guarantee a high external validity; second, the sample size was small due to the strict eligibility criteria; third, the study lacked a long-term follow-up evaluation, which could provide more information on the adherence and compliance to Denosumab therapy by the study participants.

5. Conclusion

Taken together, these findings suggest that an early starting of Denosumab treatment might be considered for the management of osteoporosis in BC postmenopausal women undergoing AIs. The present study could be considered as a starting point in this complex scenario and further studies are warranted to provide BC patients undergoing AIs with adequate indications to prevent CTIBL and its detrimental complications.

Conflict of interest

The authors certify that there is no conflict of interest in any way with any financial organization regarding the material discussed in the manuscript.

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