Letter to the Editor

Denosumab in breast cancer patients receiving aromatase inhibitors: A single-center observational study of effectiveness in adjuvant setting

Successes obtained in the treatment of women with breast cancer have also taught us the importance of simultaneously taking care of their bone health. Women with early breast cancer develop skeletal weakening due to cancer treatment-induced bone loss (CTIBL) and postmenopausal osteoporosis with a reduction of health status, quality of life, and the potential subsequent increased risk of pathological fracture. For these reasons, in patients receiving aromatase inhibitors (AI), it should be taken into account the need to add the most effective antiresorptive treatment other than the lifestyle and other modifiable risk factors changes.

A retrospective observational study on adjuvant treatment with AI and denosumab in patients with breast cancer, was conducted in our institution, according to the Helsinki Declaration, after approval by the local ethics committee and after obtaining written informed consent from each participant.

Patients received 60 mg subcutaneous denosumab every 6 months. All patients received calcium (1 g/day) and vitamin D (≥400 IU/day).

From the enrollment of the first patient (June 2015) to the cutoff date (December 2018), the duration of the study was 42 months.

The primary aim of this study was to evaluate the effectiveness of denosumab as variation of bone mineral density (BMD) and C-terminal telopeptide of type 1 collagen (CTx), at 12 months after the beginning of the therapy. Secondary objectives were the assessment of safety and tolerability of the treatment.

In all subjects, BMD measurements were performed at the time of enrollment and then each year, by using dual energy X-ray absorptiometry (DXA) (Hologic QDR 4500 W machine) at the lumbar spine and hip. BMD values were expressed as T-score, the difference (number of standard deviations) between the BMD value of the examined subject and the mean value in the healthy reference population. T-score values lower than -2.5 define osteoporosis, between -1.5 and -2.5 define osteopenia and higher than -1.5 indicates a normal BMD. Diagnosis was made according to the current criteria of the World Health Organization.[1] The CTx was dosed by blood sampling at the time of enrollment and to follow each year.

Subgroup analysis was performed among patients according to the following variables: age, type of aromatase inhibitor (steroid versus non-steroid), prior chemotherapy (yes or not), and basal T-score (≤-1.0 vs. >-1.0).

Criteria for inclusion were: age ≥18 years, histological diagnosis of breast cancer, absence of secondary disease localizations ascertained after performing clinical-instrumental tests such as chest X-ray, complete abdomen ultrasound, bone scintigraphy, total body computed tomography (CT) scan and positron emission tomography (PET) scan, hormone receptors status, adjuvant treatment with aromatase inhibitors, serum calcium corrected for albuminemia ≥8.1 mg/dL and ≤10.4 mg/dL. Previous treatment with chemotherapy and/or bisphosphonates was allowed.

Few studies have been done in a "real life setting" where patients may switch from bisphosphonates to denosumab so we have a paucity of informations in this context. Fraser *et al.*,[2] reported that the presence of secondary clinical risk factors and previous exposure to bisphosphonate do not affect the BMD response to denosumab. A greater increase in BMD and reduction in bone turnover in subjects transitioning from bisphosphonates to denosumab[3] is possible.

Exclusion criteria were: risk factors for osteonecrosis of the jaw in the oral cavity that necessitated dental intervention (avulsion, sanitation, scaling or curettage, denture reline, conservative or endodontic therapy), osteopenizing drugs intake (except AI).

A *t*-test was used to compare the groups of patients; a *P*-value <0.05 was considered statistically significant. The analysis has been carried out using the statistical software GraphPad Prism version 5.01.

A total of 68 patients were evaluated in this study.

The median follow-up of patients' population was 38 months.

The clinical features of the patients are described in Table 1.

The evaluation of changes in BMD (T-score), lumbar spine and femoral neck, and in CTx (ng/ml) from time 0 (i.e., at the beginning of treatment with AI therapy and concomitant denosumab) at the 12 month, showed that median BMD values improved, both at the lumbar spine (+2.3%, $P = 0.0005$) and at the femoral neck (+ <1%, $P = 0.0193$); as well as median CTx levels were reduced (-41.6%, $P < 0.0001$).

Subgroup analyses of the patients' population at 12 months are shown in Table 2.

Table 1: Clinical characteristics of patients

Clinical characteristics	Patients *n* (%) 68 (100%)
Average age, years	61
Median age, years	62
Range age, years	33-86
Age, years	
<60	32 (47)
60-69	20 (29)
≥70	16 (24)
Menopause	
yes	57 (84)
no	11 (16)
Histology	
Ductal	53 (78)
lobular	7 (10)
others	8 (12)
Stage	
0	1 (2)
IA	28 (41)
IB	0
IIA	18 (26)
IIB	13 (19)
IIIA	7 (10)
IIIB	0
IIIC	1 (2)
ER+/PgR+	64 (94)
ER-/PgR+ or ER+/PgR-	4 (6)
HER2	
positive	14 (21)
negative	54 (79)
Prior chemotherapy	
yes	32 (47)
no	36 (53)
Type of AI therapy	
Non-steroidal	57 (84)
steroidal	11 (16)
Basal T-score	
≤-1	58 (85)
>1	10 (15)

ER=Estrogen Receptor; PgR=Progesteron Receptor; AI=Aromatase Inhibitor

No non-traumatic fractures, osteonecrosis of the jaw, G (grade) ≥2 hypocalcemia, G3 osteoarticular pain have been reported.

No patients discontinued treatment with AI therapy and/or denosumab.

Early breast cancer patients develop bone damage secondary to cancer treatment (chemotherapy and/or hormone therapy), characterized by reduced bone mass and qualitative changes in bone structure such as the interruption of bone trabeculae, increasing the risk of fractures.[4]

The rate of bone loss depends on the fall of estrogen levels. Estrogens exert their action directly on osteoblasts increasing their number and activity, while attenuating osteoclastogenesis and stimulating osteoclast apoptosis.[5] They increase osteoblast lifespan, inhibit osteoblast apoptosis, suppress RANKL-induced osteoclast differentiation thus reducing bone remodeling, decreasing bone resorption, and maintaining bone formation.[6-9] Dysregulated autophagy is involved in several pathological processes including cancer and bone diseases[10] and inhibition of authophagy in osteoclasts preserve bone mass.[11] Other individual risk factors for bone loss should be considered, such as: age, low body mass index (BMI), previous fragility fracture, familiarity with fracture of the femur/vertebrae, smoking, alcohol habit, vitamin D deficiency, menopause before 45 years, reduced physical activity, prolonged immobilization, reduced calcium or excessive sodium intake, several diseases (chronic inflammatory, autoimmune, cirrosis, etc.) organ transplantation and related immunosuppressive therapy, use of osteopenizing drugs such as corticosteroids and several others like antiepileptics, hormonal therapy, GnRH antagonists, calcineurin inhibitors, antiretroviral drugs, selective inhibitors of serotonin reuptake, loop diuretics, heparins, oral anticoagulants, high doses of thyroxine and proton pump inhibitors, should be considered.[12,13]

Denosumab is a fully human monoclonal antibody with a high affinity and specificity for RANKL; this binding inhibits the activity of RANKL.[14]

In the study by Ellis *et al.*, early breast cancer patients with reduced bone mass (excluding osteoporosis) and on AI treatment were assigned to receive placebo versus denosumab, subcutaneously at the 60 mg dose every 6 months. At 12 and 24 months, BMD of the lumbar spine increased by 5.5% and 7.6%, respectively, in the denosumab group compared to placebo ($P < 0.0001$, in both time points). In addition, BMD increases were observed at the pelvis and femoral neck as well as the reduction of bone turnover markers in denosumab.[15]

Table 2: Subgroup analyses of the patients' population at 12 months

	Lumbar spine (T-score) median (min, max)	Femoral neck (T-score) median (min, max)	CTx (ng/ml) median (min, max)
Age (*n*)			
<65 years (43)	-2.2 (-3.7, 0.4)	-1.4 (-4.2, 0.7)	305.2 (10.0, 800.1)
≥65 years (25)	-1.9 (-3.9, 0.8)	-1.5 (-3.9, 1.0)	220.2 (70.2, 500.2)
P	0.8888	0.5907	0.1208
Type of AI therapy (*n*)			
non-steroidal (57)	-1.9 (-3.0, 0)	-1.5 (-2.8, 0.7)	124.0 (70.0, 602.3)
steroidal (11)	-2.1 (-3.7, 0.8)	-1.5 (-3.0, 1.0)	302.7 (10.0, 564.7)
P	0.7448	0.7767	0.5435
Prior chemotherapy (*n*)			
Yes (32)	-2.15 (-3.7, 0)	-1.5 (-3.0, 0.5)	400.7 (70.2, 720.0)
No (36)	-2.05 (-3.9, 0.8)	-1.5 (-4.2. 1.0)	175.5 (10.0, 800.1)
P	0.6536	0.5696	0.0113*
Basal T-score			
≤-1 (58)	-2.3 (-3.9, -0.8)	-1.6 (-4.2, -1.0)	303.9 (10.0, 800.1)
>-1 (10)	-0.05 (-1.2, 0.4)	0 (-1.7, -0.7)	145.6 (50.0, 720.0)
P	<0.001*	<0.001*	0.4992

AI=Aromatase inhibitor. *$P<0.05$

In the phase 3 ABCSG-18 trial, post-menopausal women, treated with AI, were assigned to receive denosumab 60 mg or placebo, subcutaneously, every 6 months. Compared to the placebo group, patients treated with denosumab showed significantly delayed time to the first clinical fracture regardless of baseline BMD (Hazard Ratio = 0.50, $P < 0.0001$).[16]

This retrospective observational study confirms ability of denosumab to improve the BMD values of the lumbar spine and the femur in just 12 months of treatment. The decrease in CTx that we demonstrated during denosumab therapy confirms the latter's ability to interfere with bone loss.

The safety analysis showed that treatment with denosumab during therapy with AI is well tolerated; no patient discontinued the treatment for limiting toxicity, in particular no musculoskeletal symptoms associated with aromatase inhibitors of degree ≥3 were recorded.

A limitation of our study is that it was designed as a retrospective, observational analysis, which cannot produce the high level of evidence associated with randomized, controlled trials. Its observational nature, on the other hand, allowed confirmation of safety and effectiveness of denosumab outside the selected and controlled conditions of randomized studies and the retrospective design ensures that the physician's behavior is not affected by the ongoing study.

The bone health objective gains more meaning in light of the literature data,[17,18] denosumab reduces fractures in postmenopausal breast cancer receiving aromatase inhibitors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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