

## ORIGINAL ARTICLE

# Breast cancer patients receiving denosumab during adjuvant aromatase inhibitors treatment: who are the “inadequate responders” patients to denosumab?

Azzurra Irelli<sup>1</sup>, Maria Maddalena Sirufo<sup>2,3</sup>, Teresa Scipioni<sup>1</sup>, Francesca De Pietro<sup>2,3</sup>, Amedeo Pancotti<sup>1</sup>, Lia Ginaldi<sup>2,3</sup>, Massimo De Martinis<sup>2,3</sup>

<sup>1</sup>Medical Oncology Unit, Department of Oncology, AUSL 04 Teramo, Italy; <sup>2</sup>Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy; <sup>3</sup>Allergy and Clinical Immunology Unit, Center for the diagnosis and treatment of Osteoporosis, AUSL 04 Teramo, Italy.

## Summary

**Purpose:** Adjuvant hormone therapy with aromatase inhibitors (AIs) through the induction of tissue hypo-estrogenism induces an increase in osteoclast activity and inhibition of osteoblast activity through the production of RANKL. This is a relevant cause of comorbidity in women affected by breast cancer with negative impact on quality of life. We conducted an observational study on patients treated with AIs and denosumab to compare responders and inadequate responders.

**Methods:** The study design was a historical cohort survey that represented a 42-month follow-up period for patients on hormone treatment with AI for breast cancer and concomitant denosumab (Prolia®) at 60 mg subcutaneously every 6 months. Sixty-eight patients treated consecutively at our Medical Oncology Unit were studied. The comparison was carried out by stratifying on the basis of age, body mass index (BMI), weight, carboxy-terminal collagen crosslink (CTX), lumbar spine and femoral T-scores, FRAX 10-year probability of a fracture, FRAX 10-year probability of a major osteoporotic fracture at baseline and at the end of follow-up.

**Results:** Calculating and comparing the FRAX 10-year probability of hip fragility fracture at baseline in the subgroup of responders and in the inadequate responders subgroup, we found a statistically significant difference ( $p=0.039$ ). Similarly, a statistically significant difference was found between the two subgroups of patients in terms of FRAX 10-year probability of hip fragility at the end of follow-up ( $p=0.014$ ) and FRAX 10-year probability of a major osteoporotic fracture at the end of follow-up ( $p=0.043$ ).

**Conclusion:** This study suggests the need to control weight in breast cancer survivors and adjuvant AIs treatment in order not only to reduce the incidence of disease relapse but also to safeguard bone health undergoing treatment with denosumab. Indeed, patients tend to respond inadequately to denosumab if they are not careful to control their body weight.

**Key words:** breast cancer, denosumab, osteoporosis, bone, aromatase inhibitors, skeletal health

## Introduction

The cancer treatment-induced bone loss (CT-IBL) is an iatrogenic clinical-pathological entity characterized by accelerated bone turnover, loss of bone mass, interruption of bone trabeculae and high risk of fracture with consequent negative im-

act on bone health and quality of life. Among the causes, we include adjuvant hormone therapy with AI that, through the induction of tissue hypo-estrogenism, induce an increase in osteoclast activity and inhibition of osteoblast activity through the

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Corresponding author: Massimo De Martinis, MD. Department of Life, Health and Environmental Sciences, University of L'Aquila, Piazzale Salvatore Tommasi No.1, 67100, L'Aquila, Italy.  
Tel: +39 0861 429548, Fax: +39 0861 211395, Email: demartinis@cc.univaq.it  
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production of RANKL. Tumor growth and immune regulation have a close relationship: often RANK is expressed on some cancer cells (among them some breast cancer lines) and on different “proneoplastic inflammation” cells that could express RANK [1], which favors skeletal metastasis acting as chemotactic factor. The evolutionarily conserved catabolic process of autophagy may be dysregulated in cancer, osteoporosis and several other conditions and could be target of therapy [2]. Several inflammatory cytokines play a key part in the induction of osteoporosis [3,4]. Furthermore, the increased bone turnover favors the homing of neoplastic cells to the bone that are near the osteoblast where they grow as stem cells in the so-called pre-metastatic niche [5]. Blocking RANKL bone resorption is inhibited, proneoplastic inflammation decreased, tumor growth diminished and apoptosis of malignant cells enhanced [1]. Antiresorptive drugs avoid the CTIBL. It is recommended a daily intake of 1200-1500 mg of calcium, preferably through the diet and 400-800 IU of vitamin D a day. In clinical practice, we monitor and evaluate the success of these therapies in two ways: through clinical follow-up and measuring surrogate markers such as Body Mass Density (BMD) and bone turnover markers such as CTx. Some individuals do not respond adequately to antiresorptive drugs. Fracture is the main pathological event of the CTIBL and a cause of morbidity. Furthermore, fracture is one of the most powerful predictors of subsequent fracture risk. No antiresorptive therapies completely prevents fractures. A treatment can also be effective in a patient who suffers a fracture. The appearance of a fracture is not a sufficient criterion to define an inadequate response to treatment [6]. The prevalence of inadequate response is discordant, ranging from 9.5 to 53% among the different studies. These different percentages could be due to the different criteria for defining the response to antiresorptive drugs among the different studies, based on a decrease in BMD that exceeds a specific threshold after a given treatment period, or on the appearance of new fractures, or both criteria [7]. The response can be classified as inadequate for fracture and decrease in BMD greater than 2%; possibly inadequate for fracture or decrease in BMD greater than 2%; and adequate in case of no fracture and no decrease in BMD greater than 2%.

The evaluation has been carried out in an observation interval of 1 to 2 years according to the committee of the International Society of Clinical Densitometry. The prediction of an appropriate response in an individual could come from pharmacogenomics, such as the P2X7 Glu496Ala and the Ile568Asn single nucleotide polymorphisms, the

Glu496Ala polymorphism [8], the determination of ERalpha, PP and XX genotypes [10], a specific SNP and the haplotype of the selected SNP [11], the A2 allele of the CYP17 T(27)-C polymorphism [12], and genetic variation at the VDR locus [7,13]. Many authors have identified the presence of secondary osteoporosis and/or hypovitaminosis D or poor compliance as the factors that could determine an inadequate clinical outcome with antiresorptive therapies [13]. The possible additional factors associated with an inadequate response to antiresorptive treatments are unknown [8].

However, non-skeletal risk factors that predict failure should be considered: chronic conditions, such as arthritis and other musculoskeletal disorders, visual impairment, hearing problems, proprioceptive impairment, previous history of falls, poor gait, poor balance, dementia or confusion, smoking; and acute conditions, such as infections, strokes, cardiovascular events, drugs (sedatives, psychotropic drugs and other drugs, including alcohol), postural hypotension and delirium. Siminoski et al [14] found that the height loss is related to new vertebral fractures and an increased number of vertebral fractures. A loss in height of 2 cm or more, within 3 years, has a sensitivity of 35.5% and a specificity of 93.6% [15].

Denosumab, a fully human monoclonal antibody (MAB), binds to the receptor activator of the NF- $\kappa$ B ligand (RANKL) and blocks the stimulation of RANK, thus inhibiting the activity and survival of osteoclasts. The positive effects of denosumab are related to increased cortical volume and bone mineral content at the femur, converting the trabecularized cortical bone into denser cortical bone [16].

Roux et al found that even after bisphosphonate treatment, denosumab had greater inhibitory effects on bone resorption and BMD stimulatory effects, confirming that denosumab produces a much more pronounced inhibition of bone resorption [17,18].

In breast cancer patients receiving adjuvant AIs reduced BMD (excluding osteoporosis), denosumab, subcutaneously at a dose of 60 mg every 6 months, has been shown to increase lumbar spine BMD by 5.5% and by 7.6%, at 12 and 24 months, respectively (versus placebo,  $p < 0.0001$  at both time points). Also the BMD at the pelvis and neck of the femur was increased and the bone turnover markers were reduced [19]. In this patient setting, denosumab has also been shown to delay the onset of clinical fracture independently of baseline BMD (HR=0.50,  $p < 0.0001$ ) [20]. Therefore, national and international guidelines recommend starting anti-absorptive therapy in conjunction with hormone therapy (note 79 according to the AIFA) [21]. Stud-

ies on denosumab in breast cancer patients receiving adjuvant AIs treatment have followed studies on the efficacy of denosumab in the treatment of osteoporosis in postmenopausal women.

In the setting of patients with osteoporosis, denosumab demonstrated a statistically significant advantage, versus placebo, in reduction of new radiographic vertebral fracture (2.3% in the denosumab group, compared to 7.2% in the placebo group ( $p < 0.001$ ) with decrease relative 68%), reduced risk of hip fracture (0.7% cumulative incidence in the denosumab group versus 1.2% in the placebo group ( $p = 0.04$ ) and 40% reduction) and reduction of the risk of non-vertebral fractures (a cumulative incidence of 6.5% in the denosumab group compared to 8.0% in the placebo group ( $p = 0.01$ ) with a relative decrease of 20%) [22]. McCloskey et al demonstrated that the efficacy of denosumab was greater in postmenopausal women with moderate to high fracture risk as assessed by FRAX® [23,24].

The FRAX® computerized algorithm (available at [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)) is a fracture risk assessment tool developed by the University of Sheffield (United Kingdom). FRAX combines several clinical risk factors (country, age, sex, weight, height, previous fractures, family history of fractures, smoking, treatment with glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, alcohol intake, with or without evaluation of BMD at the neck of the femur), to assess the probability at 10 years of hip fracture and of important osteoporotic fractures (fracture of the vertebral column, forearm, hip or shoulder) [25].

It would be interesting to evaluate the applicability of FRAX in determining the efficacy of denosumab in breast cancer patients treated with AIs. In the literature studies have not been published on the subject.

Then there is the whole line of research regarding the evaluation of the impact of denosumab on DFS. Current national and international guidelines do not indicate using denosumab to increase DFS [5,26,27].

## Methods

### Study design

The study design was a historical cohort survey that represented a 42-month follow-up period for patients on hormone treatment with AI for breast cancer and concomitant denosumab (Prolia®) at 60 mg subcutaneously every 6 months. From June 2015 to December 2018, we selected the medical records of 68 patients treated consecutively at our Medical Oncology Unit. All patients received calcium (1 g/day) and vitamin D ( $\geq 400$  IU/day).

This longitudinal observational study compared re-

sponders with inadequate responders, the latter selected based on a BMD value  $\geq 2\%$ . The comparison was carried out by stratifying on the basis of age, body mass index (BMI), weight, CTx at the baseline and at the end of follow-up, lumbar spine T-scores at the baseline and at the end of the follow-up, femoral T-score at the baseline and at the end of follow-up, FRAX 10-year probability of a fracture at baseline and at the end of follow-up, FRAX 10-year probability of a major osteoporotic fracture at baseline and at the end of follow-up.

CTx was determined by blood sampling at the time of enrollment and followed by 18 months of denosumab treatment.

The BMD, in terms of T-score, was measured with the calcaneal bone densitometer at the time of enrollment and followed at 18 months of treatment with denosumab.

All patients provided written informed consent to the study and to data collection from existing clinical medical records. This study was retrospective observational, and did not affect the relationship between clinicians and patients or standard patient follow-up patterns. The study was approved by the Internal Review Board of the University of L'Aquila, Italy, (ex "Comitato etico di Ateneo" D.R. n. 206/2013 modified D.R. n. 46/2017) "Ginaldi 15/04/2014" (<http://www.univaq.it/include/>

**Table 1.** Clinical characteristics of patients

Characteristics	Patients n (%)
Median age, years	61
Range age, years	33-86
Menopause	
Yes	57 (84)
No	11 (16)
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)

utilities/blob.php?item=file&table=allegato&id=1925) and conducted in accordance with the 1975 Helsinki Declaration and its subsequent amendments.

#### Patient eligibility

**Inclusion criteria were:** age  $\geq$  18 years, histological diagnosis of breast cancer, absence of metastases (ascertained after clinical-instrumental examinations such as chest X-ray, complete abdomen ultrasound, bone scintigraphy and possible total-body CT scan and/or  $^{18}\text{F}$ FDG-PET), positive hormone receptors, adjuvant AIs treatment, serum calcium adjusted for albuminemia  $\geq$  8.1 mg/dl and  $\leq$  10.4 mg/dl. Previous chemotherapy was permitted.

**Exclusion criteria were:** previous fragility fractures, parents with a history of fragility fractures, history of smoking, alcohol abuse, cortisone intake, history of rheumatoid arthritis or secondary osteoporosis, and risk factors for osteonecrosis of the jaw oral cavity that required dental surgery (avulsion, sanitation, scaling/curettage, denture, conservative/endodontic therapy).

#### Statistics

Statistical analyses were performed using Student's *t*-test when comparing continuous variables, and  $\chi^2$  test when comparing categorical variables, in Microsoft Excel. Values of  $p < 0.05$  were considered significant.

## Results

#### Patient features

A total of 68 patients were considered in the present study.

The median patient age was 62 years;  $< 60$  years, 32 (47%); 60-69 years, 20 (29%);  $\geq 70$  years, 16 (24%). Menopausal status in 57 patients (84%). Histology of the primary tumor: ductal, 53 (78%); lobular, 7 (10%); other, 8 (12%). Disease stage: 0, 1 (2%); IA, 28 (41%); IIA, 18 (26%); IIB, 13 (19%); IIIA, 7 (10%); IIIC, 1 (2%). According to the immunohistochemical profile of the primary tumor, we identified the following subgroups: ER + / PgR +, 64 (94%); ER- / PgR + or ER + / PgR-, 4 (6%); HER2 +, 14 (21%); HER2-, 54 (79%). Previous chemotherapy was administered to 32 patients (47%). The type of AIs was: steroid, 11 (16%); non-steroid, 57 (84%).

The median time to AIs treatment was 38 months.

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

#### Efficacy

Bone health characteristics of all patients

**Table 2.** Characteristics related to bone health of all patients, responders and inadequate responders during denosumab

	All patients n=68	Responders n=43 (63%)	Inadequate responders n=25 (37%)	p value
BMI at baseline	26.17 (17.65; 43.50)	25.07 (19.72; 43.50)	27.10 (17.65; 35.56)	0.34
Body weight at baseline (kg)	68.00 (48.00; 117.00)	68.00 (45.00; 117.00)	68.00 (50.00; 81.00)	0.44
CTX at baseline	606.75 (31.10; 1452.30)	523.20 (31.10; 1452.30)	724.60 (125.30; 1249.00)	0.06
CTX at the end of follow-up	252.15 (10.00; 800.10)	236.20 (10.00; 800.10)	302.70 (66.99; 720.00)	0.44
Lumbar spine T-score at baseline	-2.15 (-4.70; 0.70)	-2.50 (-4.70; 0.70)	-1.50 (-4.00; -0.20)	0.07
Lumbar spine T-score at the end of follow-up	-2.10 (-3.90; 0.80)	-2.20 (-3.90; -2.20)	-1.60 (-1.50; -0.10)	0.39
Femoral T-score at baseline	-1.50 (-6.60; 0.70)	-1.50 (-6.60; 0.70)	-1.50 (-2.50; 0.60)	0.10
Femoral T-score at the end of follow-up	-1.50 (-4.20; 1.00)	-1.50 (-4.20; -1.50)	-1.50 (-3.10; 0.50)	0.31
FRAX 10-year probability of a hip fragility fracture at baseline	19.00 (0.20; 45.00)	17.00 (0.20; 21.00)	28.00 (0.20; 45.00)	0.04
FRAX 10-year probability of a major osteoporotic fracture at baseline	16.00 (2.80; 54.00)	15.00 (2.90; 40.00)	22.00 (2.80; 54.00)	0.21
FRAX 10-year probability of a hip fragility fracture at the end of follow-up	12.00 (0.10; 47.00)	11.00 (0.10; 19.00)	18.00 (0.10; 47.00)	0.01
FRAX 10-year probability of a mayor osteoporotic fracture at the end of follow-up	16.00 (2.90; 56.00)	15.00 (2.90; 32.00)	19.50 (2.90; 56.00)	0.04

and responders versus inadequate responders are shown in Table 2.

### Safety

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

No patient discontinued treatment with AI and/or denosumab.

## Discussion

The FRAX tool, in the absence of previous fragility fractures, familiarity for fragility fractures, history of smoking, alcohol abuse, cortisone intake, history of rheumatoid arthritis or secondary osteoporosis, is a tool that combines the BMI of patients with their BMD.

Calculating and comparing the FRAX 10-year probability of hip fragility fracture at baseline in the subgroup of responders and in the subgroup of inadequate responders, a statistically significant difference was revealed ( $p=0.039$ ). Similarly, a statistically significant difference was found between the two subgroups of patients in terms of FRAX 10-year probability of hip fragility at the end of follow-up ( $p=0.014$ ) and FRAX 10-year probability of a mayor osteoporotic fracture at the end of follow-up ( $p=0.043$ ).

Therefore, it is clear the importance of leading a correct lifestyle, through adequate physical activity and a suitable diet.

The reasons for weight gain are multifactorial and include "stress eating", reduced activity due to fatigue or other adverse effects related to treatment or reduction of chemotherapy metabolism and use of pre- and post-chemotherapy drugs such as dexamethasone. Weight gain is more common to induction of menopause and is accompanied by relative gain of fat and muscle loss. Several observational studies have shown that weight gain during or after treatment with breast cancer increases the risk of relapse and reduces survival, regardless of baseline body mass index (BMI) [28-30]. Exercise leads to improvements in physical functioning, in quality of life [31] and in the psychological functioning of cancer survivors. Patients should be advised to avoid inactivity and take at least 150 min of moderate intensity aerobic exercise and 2-3 moderate intensity resistance training sessions each week [32]. The greatest benefit occurred in patients who performed the equivalent of walking 3 to 5 h a week

at an average pace [33]. This recommendation was approved by the Canadian Cancer Society and by the American Cancer Society. However, more hours of exercise could have a greater benefit. Patients who gain weight during or after breast cancer treatment have been constantly exposed to a higher risk of death related to breast cancer [34]. Mechanisms that cause obesity can affect breast cancer mortality including an increase in the growth factor similar to circulating insulin, high levels of circulating sex hormones and production of pro-inflammatory cytokines. Another possible mechanism is the metabolic syndrome defined by the presence of at least three of the following conditions: central obesity defined as waist circumference  $>88$  cm, arterial hypertension with value  $\geq 130/85$  mmHg, increase in triglyceridemia  $> 150$  mg/dl, reduction in levels of HDL cholesterol  $<50$  mg / dl and blood glucose  $\geq 110$  mg/dl [35].

Alongside appropriate physical activity, nutritional education seems to reduce the risk of incidence of recurrence to breast cancer [36]. The intake of at least 400 g/day of fruit and vegetables and no more than 500 g/week of red or preserved meat. Reduced consumption of food for animals (-43.9%) and alcohol (-0.2 g of ethanol/day) and increased food intake in plants (+ 65.4%) [37].

The main limitations of this study are the small number of the enrolled patient population, the retrospective nature of the analysis and the relatively short follow-up period.

## Conclusion

This study suggests the need to control weight in breast cancer survivors and adjuvant AIs treatment in order not only to reduce the incidence of disease relapse but also to safeguard bone health undergoing treatment with denosumab. Indeed, patients tend to respond inadequately to denosumab if they are not careful to control their body weight.

## Authors' contributions

Conception and design, collection and assembly of data, manuscript writing: all authors. All authors approved the final version.

## Conflict of interests

The authors declare no conflict of interests.

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