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Denosumab for Cancer Related Bone Loss

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Abstract

Introduction:

Prolonged use of anti-cancer treatments in breast and prostate tumors alters physiological bone turnover leading to adverse skeletal related events, such as osteoporosis, loss of bone mass and increased risk of fractures. These complications known as cancer treatment-induced bone loss (CTIBL) should be managed with bone targeting agents such as the bisphosphonates and denosumab. The latter is a monoclonal antibody against the receptor activator of nuclear factor- κ B ligand (RANKL) that suppresses osteoclasts function and survival increasing bone mass.

Areas Covered

This review will focus on the mechanisms associated with bone loss induced by cancer treatments and the most recent evidence about the use of denosumab as preventive and therapeutic strategy to protect bone

health. Moreover, we will discuss several key aspects regarding the clinical practical use of denosumab to optimize the management of CTLIB in breast and prostate cancer.

Expert Opinion

Denosumab treatment strongly prevents cancer therapies-related skeletal issues in breast and prostate cancer with a good safety profile. Adjuvant six-monthly denosumab delays the time to first fracture onset in early stage breast cancer patients with normal or altered bone mineral density (BMD). Similarly, denosumab treatment is able to prevent fractures and BMD loss in non-metastatic prostate cancer patients.

Keywords: Cancer Treatment Induced Bone Loss (CTLIB), denosumab, bone health, osteoporosis

Article Highlights

- Treatment induced bone loss increases fracture risk and requires the use of a bone targeted agent in addition to lifestyle modifications.
- Denosumab treatment in breast and prostate cancer patients reduces the time to first fracture and increases bone mineral density.
- Denosumab is recommended in breast cancer patients treated with hormonal therapy and prostate cancer patients receiving Androgen Deprivation Therapy (ADT) for >6 months with either a BMD T score of <-2 or with ≥2 risk factors for fractures.
- Denosumab is non-inferior to zoledronic acid in preventing first Skeletal Related Event (SRE) in patients with multiple myeloma with a comparable safety profile.
- Denosumab is well tolerated, even if the duration of treatment remains controversial.

1. Introduction

Bone health is a clinically relevant issue for cancer patients, especially those with breast and prostate tumors.

Cancer patients can experience an increased bone loss due not only to the direct effects of cancer on the skeleton, but also to the use of some anti-cancer treatments that alter physiological bone turnover worsening its integrity.

It has been widely demonstrated that endocrine therapy and chemotherapy can adversely affect bone health in breast and prostate cancers, leading to the so-called cancer treatment-induced bone loss (CTIBL) [1].

Bone loss is caused by an increased osteoclast (OC) differentiation and activity mainly due to a dysregulation of receptor activator of nuclear factor- κ B ligand (RANKL)/ RANK pathway. In particular, a rise of RANKL activity enhances bone turnover, reduces bone mineral density (BMD), resulting in skeletal fragility and osteoporosis [2].

Denosumab is a fully humanized monoclonal antibody that specifically targets RANKL, inhibiting OC mediated bone resorption [3]. Under the brand name Prolia® (60 mg every 6 months), it is approved for treatment of postmenopausal women with osteoporosis and in breast and prostate cancer patients, at high risk for fracture, receiving hormone ablation therapy. In addition, denosumab, marketed as XGEVA (120 mg every four weeks), is indicated for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors. SREs, that include pathological fractures, spinal cord compression, radiation for severe bone pain, hypercalcemia of malignancy, surgery to bone, negatively affect patients' quality of life, reducing mobility, social functioning and overall survival (OS) [4].

In this review, we will discuss the role of denosumab as treatment to reduce the incidence of fractures and bone loss associated with cancer treatments, especially in breast and prostate cancer patients.

2. Bone health actors and osteoporosis

The skeleton is a dynamic organ in a constant state of remodeling, which is fundamental for the maintenance of normal bone structure and function. Bone health depends on the cross-talk between many types of cells, different cytokines, hormones and signaling pathways showed in **figure 1**.

2.1 Bone cells

Bone remodeling is a tightly regulated process mediated by the balance of bone resorbing OCs and bone forming osteoblasts (OBs) [5]. OCs originate from hematopoietic progenitors and differentiate under the influence of several factors including macrophage-colony stimulating factor (M-CSF), RANKL and osteoprotegerin (OPG) [6]. The latter two, secreted by OBs, competitively bind their receptor RANK promoting or inhibiting osteoclastogenesis, respectively [7]. OBs differentiate from mesenchymal stem cells in bone marrow and are essential for bone anabolic processes. OBs maturation is regulated by multiple growth factors, receptors, and transcriptional factors some of which are Runt-related transcription factor 2 (Runx2), Fibroblast Growth Factors (FGFs), Parathyroid Hormone (PTH) and osterix [8]. Osteocytes, derived from embedded OBs in bone matrix, function as mechanosensors and play a crucial role in physiological and pathological bone remodeling [9]. Indeed, they are the major source of RANKL in adult bone and, therefore, the principal regulators of OC differentiation [10]. Recent evidences suggest that the crosstalk between osteocytes and tumor cells generate a microenvironment that promote cancer cells survival and stimulates bone destruction [11]. Indeed, preclinical studies demonstrated that myeloma cells

induced RANKL production in osteocytes and, concomitantly, reduced OPG expression, thus increasing bone loss [12]. Moreover, sclerostin, mainly produced by osteocytes, are increased in breast and prostate cancer patients receiving hormone therapies and these high levels are associated with skeletal disease [13]. Bone remodeling is also regulated by the dynamic interaction between bone cells and the lymphocytes residing within the bone marrow. Activated T lymphocytes can promote bone resorption through RANKL [2] and Tumor Necrosis Factor- α (TNF- α) secretion, [14] but, in some cases, possess anti-osteoclastogenic properties. Indeed, in the pathogenesis of osteoporosis, Th1 and Th2 cells produce different cytokines that can inhibit osteoclastogenesis preventing bone loss [15-18]. Similarly, regulatory T cells inhibit OC differentiation, acting directly on bone and/or inhibiting Th17 cells in inflammation-induced bone loss [19].

2.2 Sex steroids

Both androgens and estrogens, as well as other reproductive hormones have crucial roles in the preservation of bone health. In particular, androgens promote OB differentiation and activity and, simultaneously, inhibit OC precursors, blocking RANKL-induced signalling [20-22]. The anabolic and anti-resorptive effect of androgens is also mediated by the modulation of specific growth factors, such as the upregulation of Insulin-like Growth Factor (IGF) and Transforming Growth Factor beta (TGF β) and the downregulation of Interleukin-6 (IL-6) [23]. Since androgens are important and required for skeletal health, their deprivation induced by cancer treatments, leads to high-turnover and osteoporosis. In particular, in Androgen Deprivation Therapy (ADT)-mediated bone loss, both trabecular and cortical bone are affected, resulting in a decrease in BMD and disruption of bone integrity [24-25].

Similar to androgens, estrogens promote bone formation through Estrogen Receptor alpha and beta (ER α and ER β), both expressed by OBs and OCs. In particular, estrogens preserve skeletal integrity stimulating OB differentiation and OC apoptosis, while their deficiency increases the rate of osteocyte death, causing bone fragility [26-28]. In women at the menopause, the significant fall in circulating estrogens, alters bone remodelling with increased loss of bone mass and strength. Estrogens are critical for the maintenance of normal bone structure also in men, where their decline accelerates bone turnover and osteopaenia [29]. The estrogens can directly influence immune system response inhibiting the secretion of pro-inflammatory cytokines, including IL-6 and TNF α from monocytes and repressing Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) transcriptional activity [30]. Estrogen deprivation leads to dramatic elevations in the number of basic multicellular units (BMUs) that increase cortical porosity and extend the resorption area on trabecular surfaces. This phenomenon is due to a complex interplay of estrogens and cytokines that converge to an increase of OC lifespan and recruitment to bone surfaces [31-32]. Moreover, the increase in new bone deposition induced by estrogen deficiency that is accompanied by an augmentation in OB apoptosis is inadequate to compensate the enhanced bone resorption [33]. In

addition, the elevated production of inflammatory cytokines, following estrogen deprivation, rises the apoptotic rate of mature OB limiting their activity [34-35].

2.3 Calcium and Vitamin D

Bone stores more than 99% of the body's calcium that provides the skeletal strength and integrity. Calcium homeostasis is tightly regulated through an integrated hormonal system that involves PTH and 1,25-dihydroxyvitamin D [1,25(OH)₂D], the active form of vitamin D. A fall in serum calcium stimulates PTH secretion which activates the parathyroid receptor (PTHr) leading to the release of calcium in bone and an increased tubular calcium reabsorption in kidney. Moreover, in the kidney, PTH stimulates the secretion of 1,25(OH)₂D that, through the vitamin D receptor (VDR), promotes bone resorption and an increased calcium absorption in gut. With a rise in serum calcium, the integrated hormonal response reversed these actions through negative feedback mechanisms [36-38].

The appropriate intake of calcium and vitamin D in diet have proven its efficacy in maintaining normal bone growth during the adolescence and preventing age-related osteoporosis [39]. Abnormally low and high serum calcium concentrations are clinically referred as hypercalcemia and hypocalcemia, respectively. Disruption of bone remodelling by disease that cause excessive bone resorption such as osteoporosis, bone metastatic cancers and primary hyperparathyroidism, results in hypercalcemia. Conversely, an increased in bone formation that occurs in osteoblastic metastatic bone cancers and in postparathyroidectomy "hungry bone syndrome" is responsible of hypocalcemia

Concerning the relationship between vitamin D and bone health, several studies reported that inadequate vitamin D intakes over long periods can lead to a reduction of BMD. Indeed, Vitamin D deficiency increases bone turnover to maintain circulating calcium concentrations with consequent bone weakening, increased risk of fractures and osteoporosis [40]. In addition, vitamin D can influence bone health through the modulation of pro-inflammatory cytokines often associated to higher bone metabolism [41].

All patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium-enriched diet and take 1000-2000 IU vitamin D every day. If a calcium-enriched diet and vitamin D are not sufficient, guidelines recommend a daily supplements of calcium (1000-1200 mg) and vitamin D3 (800-2000 IU) [I, B]. Moreover, correction of vitamin D deficiency and adequate intake of calcium are also recommended during bisphosphonates [I, B] and denosumab [I, A] treatment [42].

2.4 Osteoporosis

Osteoporosis is a disease characterized by reduction in bone mass and alteration of bone tissue architecture and it is defined by ≤ 2.5 standard deviation BMD at the hip or lumbar spine compared to mean BMD of a young-adult population [43]. BMD measure should be performed in women aged at least 65 years old, in men aged at least 70 years old, in postmenopausal women and in men aged 50-69 years old

with risk factors or anamnesis of adult age fracture [44]. Single vertebral fracture predicts higher risk of future vertebral, hip and other fractures [45], thus vertebral imaging is suggested for:

- women aged at least 70 and in men aged at least 80 if BMD T-score is ≤ -1.0 at the spine, total hip or femoral neck,
- women between 65 and 69 years old and men between 70 and 79 years old if BMD T score is $\leq$ at the spine, total hip or femoral neck,
- postmenopausal women and men aged at least 50 when concurrent risk factors are present: low-trauma fracture in adult age, significant height loss (difference between current height and peak height at age 20), prospective height loss (difference between current height and previous measurement) and long term glucocorticoid treatment [44].

Cancer-induced inflammation and hormonal cancer treatments, such as gonadotropin-releasing hormone (GnRH), ovarian failure inducing chemotherapy, aromatase inhibitors (AI) [46-48] and antiandrogens are the most common agents inducing osteoporosis in cancer patients [49-50]. Particular attention to osteoporosis screening in nonmetastatic cancer patients should be guaranteed in presence of critical risk factors, such as advanced age [51], current cigarette smoking, high alcohol consumption [52], history of prior nontraumatic fractures in adulthood, hypogonadism, impaired mobility, increased risk for falls, long term exposure to glucocorticoids, low body weight [53], parental history of hip fracture and postmenopausal status. BMD evaluation with central/axial dual-energy x-ray absorptiometry (DXA) or alternatively quantitative ultrasound or calcaneus DXA should be offered when single or multiple factors are pointed out [54]. If the patient receives a bone loss inducing treatment, BMD testing should be assured at least every 2 years [54].

Once excluded causes of secondary osteoporosis, pharmacological treatment with oral or intravenous bisphosphonates or subcutaneous denosumab should be assured for postmenopausal women and men aged at least 50 years old:

- with hip or vertebral fracture, since it correlates with higher risk of future fracture and major benefit from pharmacological therapy [55-58],
- when T score is ≤ -2.5 at the femoral neck, total hip or lumbar spine [59-60],
- if T score is between -1.0 and -2.5 at the femoral neck or lumbar spine and 10-year probability of hip fracture is $\geq 3\%$ or 10-years probability of major osteoporosis-related fracture is $\geq 20\%$ [61-62].

Both bisphosphonates and denosumab are recommended in bone metastatic breast and prostate cancers [63].

In particular, zoledronic acid guaranteed lower risk of skeletal complication in comparison with pamidronate [64] and oral ibandronate [65] in metastatic breast cancer, even though denosumab treatment showed lower risk and delayed time to first skeletal event compared to zoledronic acid [66] with better outcomes on quality of life [67] and pain reduction [68].

3. Bone loss in breast cancer

3.1 The effect of chemotherapy on bone loss

Thanks to outstanding treatment improvements (including surgery, chemotherapy, radiation, HER2-targeted treatment, and endocrine therapy), breast cancer survival has improved over time and is now around 85% at 5-year [69]. Given this, preventing the long-term morbidity derived from breast cancer treatments is of the utmost importance in order to reduce late impairments in breast cancer survivors, especially those related to bone health. Both direct and indirect drug effects may cause chemotherapy-induced bone loss. Preclinical studies have hypothesized direct cytotoxic interference on OBs and OCs, showing a detrimental effect on bone turnover, but robust clinical data are still lacking [1].

Moreover, chemotherapy may exert an indirect harmful effect by damaging gonadal function and by leading to premature endocrine deprivation [70-71]. The biological mechanism is believed to be secondary to a rapid drop in estrogen levels due to chemo-induced ovarian failure and this observation has been clearly demonstrated for pre-menopausal patients in the clinical setting [72].

Different mechanisms underlying chemo-induced bone loss can explain why pre-menopausal patients showed much higher BMD changes against post-menopausal ones. A drop rate around 3% to 7% in the lumbar spine and 2% to 4% in the total hip have been demonstrated for women who lost their menses due to chemotherapy, especially in the very first 6 months from treatment beginning [70]

In a retrospective cohort study involving 492 patients with early breast cancer, premenopausal women had a significantly larger loss of BMD in the lumbar spine than postmenopausal women in the univariate analysis, addressing the clinical need for population-specific prevention strategies even if hormone-therapy is not scheduled [73].

In postmenopausal women, chemotherapy has not been studied extensively as an independent factor for bone loss, although it has been associated with lower BMD in a small retrospective analysis [74].

Recently, no association was found between chemotherapy and fracture incidence in this population, suggesting a minor effect when low estrogen status has already physiologically been reached [75].

The use of antiresorptive therapies, as bisphosphonates and denosumab, is less extensively proven in patients undergoing chemotherapy regardless from following hormone therapy. Oral clodronate has shown the ability of reducing the amount of bone loss associated with chemotherapy, but persistent BMD decrease of 2.2% at 2 years limited its clinical impact [76]. By contrast, zoledronic acid at 4 mg intravenously every 3 months for 12 months during the first year of chemotherapy was able to stabilize BMD representing an effective and well-tolerated strategy in this clinical setting for future indication [77].

3.2 The effect of endocrine therapy on bone loss

Several guidelines recommend that women with breast cancer receiving an AI therapy or ovarian suppression should have their bone health monitored for fracture risk [54,78].

The consensus from expert panels recommends treatment with Bone Target Agents (BTA) in patients receiving AI therapy with a T-score below -2.0 or two or more clinical risk factors for fracture [79]. Moreover, BMD is not the only risk parameter but an overall assessment should be carried out which gives a real estimate of the risk [78].

Premenopausal patients often receive treatments tailored to suppress circulating estrogen levels. In addition to bone loss associated with low oestrogen levels, cytotoxic chemotherapy and tamoxifen may have direct negative effects on bone metabolism [50]. The current methods of diagnosis are often set on post-menopausal patients; an overall assessment of premenopausal patients undergoing hormone treatment for early breast cancer is therefore necessary, who must be correctly informed and sent for treatment with agents inhibiting osteoclastic activity in case of the BMD T-score is <-2 [78,80].

Data from randomised clinical trials in >5000 patients show that bisphosphonates (both i.v. and oral) and denosumab, administered at doses and schedules that approximate to those used for the treatment of postmenopausal osteoporosis, can prevent bone loss in women with breast cancer [54,78].

Denosumab 60 mg once every 6 months, in addition to adequate calcium and vitamin D supplementation, reduced fractures by 50% compared with placebo, providing the best evidence to date for the use of a BTA for preservation of bone health in early breast cancer. This effect was somewhat independent from age and BMD at baseline [81]. In addition to preventing SRE in the oncology setting, denosumab is indicated for fracture risk reduction also in elderly cancer patients with osteoporosis [82].

3.2.1 Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer: from fracture reduction to disease-free survival

Early diagnosis and the introduction of effective therapies have reduced breast cancer mortality. Patients with positive hormone receptors are treated with adjuvant hormonal therapies to reduce the recurrence rate; they include estrogen receptor modulators (SERMs; e.g., tamoxifen), AIs (e.g., letrozole, anastrozole, exemestane), and luteinizing hormone-releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide).

In post-menopausal women, AIs are the standard of care for hormone receptor-positive (HR+) early-stage cancer, but its use is associated with several side effects including osteoporosis, loss of bone mass and increased fracture risk. Indeed AIs suppress the conversion of androgens to estrogens, resulting in estrogen depletion, which in turn leads to lower BMD and increased fracture risk [83].

Two large studies have evaluated the efficacy of denosumab in improving bone health in patients with non-metastatic breast cancer during adjuvant treatment with AIs. Based on the results of denosumab in patients with osteoporosis, Ellis et al. planned a phase III study aimed to identify the efficacy of denosumab

in patients with non-metastatic breast cancer during adjuvant treatment with AIs [84]. In particular, 252 post-menopausal patients undergoing to adjuvant hormone treatment were enrolled in this study; denosumab administered for two years conferred a 6.2% increase in lumbar BMD and in all bone sites examined, regardless of the duration of hormone therapy. In this study the safety profile was similar in the two arms and no specific side effect pattern was identified for the experimental group. In conclusion, in women with nonmetastatic breast cancer who were receiving adjuvant AI therapy and who were at risk of developing osteoporosis and fracture, twice-yearly treatment with denosumab was generally well tolerated, with an adverse event (AE) profile similar to that of placebo, and significantly increased BMD and reduced bone turnover.

A more recent study enrolled 3420 women to receive denosumab vs placebo every six months during adjuvant AIs therapy, to identify the time to the first clinical fracture [85]. Compared with the placebo group, patients in the denosumab group had a significantly delayed time to first clinical fracture (HR= 0.50 [95% CI 0.39-0.65], $p<0.0001$). The overall lower number of fractures in the denosumab group (92) than in the placebo group (176) was similar in all patient subgroups, including in patients with a BMD T-score of -1 or higher at baseline ($n=1872$, HR= 0.44 [95% CI 0.31-0.64], $p<0.0001$) and in those with a BMD T-score of less than -1 already at baseline ($n=1548$, HR=0.57 [95% CI 0.40-0.2], $p=0.002$).

The safety profile was comparable between the two groups and no serious adverse event was thought to be attributed to denosumab.

Results from the ABCSG-18 trial showed that use of denosumab as an adjuvant to AI therapy significantly reduced clinical fractures. The secondary endpoint of the study was the disease free survival (DFS); DFS was significantly improved in the denosumab group versus the placebo group (HR= 0.82, 95% CI 0.69–0.98, $p=0.0260$; descriptive analysis, without controlling for multiplicity). In the denosumab group, DFS was 89.2% (95% CI 87.6–90.8) at 5 years and 80.6% (78.1–83.1) at 8 years of follow-up, compared with 87.3% (85.7–89.0) at 5 years and 77.5% (74.8–80.2) and 8 years in the placebo group. With the results of this study we can say that denosumab constitutes an effective and safe adjuvant treatment for patients with postmenopausal hormone receptor-positive early breast cancer receiving AI therapy.

The osteoporosis schedule of denosumab was evaluated by the ABCSG in a study primarily aimed at assessing the agent's ability to prevent bone loss and fractures associated with the use of AIs [81].

A significant improvement in DFS was reported but the apparent benefits of denosumab seemed to be driven more by effects on second non-breast primary cancers and deaths without recurrence, than prevention of breast cancer recurrences; effects that seem biologically implausible [86]. Up to date, no overall survival benefit has been clearly demonstrated for adjuvant denosumab and the goal of this treatment remain bone-loss prevention instead of altering breast cancer disease course.

4. Denosumab and Prostate Cancer

Prostate cancer is the most frequent cancer and the fifth leading cause of cancer death in men [87]. ADT is the mainstay of treatment of prostate cancer, both in localized [88] and in metastatic setting [89]. ADT includes orchiectomy, GnRH agonists (e.g., leuprolide, goserelin) and antagonists (e.g., degarelix), given either alone or in combination with androgen receptor antagonists (e.g., flutamide, bicalutamide, nilutamide [88]).

The prevalence of osteoporosis and osteopenia before treatment with ADT ranges between 35% and 58% and remains undiagnosed in the majority of cases [90]. The rate of bone loss is approximately 0.5-2% per year, but after the start of ADT, this value increases reaching 4-4.6% per year [91-93]. Indeed, ADT suppresses testosterone levels to a castration range of values (<5% of the normal range) and serum estradiol levels to <20% of the normal range [94] leading an accelerated loss of BMD, an increase of bone resorption and fracture rate, as evidenced by large retrospective epidemiological studies [95-96].

Prostate cancer patients treated with ADT, alive at least five years after diagnosis, had a significantly higher percentage of fracture (19.4% vs 12.6%, $P<0.001$) than those who do not receive ADT, and the fracture risk increased with the number of ADT doses administered during the first year after diagnosis [97], as a consequence of the rapid damage due to elevated bone turnover. It is worth noting that the addition of bicalutamide to GnRH agonists did not worsen BMD loss compared to GnRH agonists alone [98] neither that the intermittent ADT in older men reduced the rate of bone events (26% vs 31%, respectively, $P=0.15$) [99-100]. For these reasons, prostate cancer patients treated with ADT should have bone health monitored for fracture risk [54,78].

The World Health Organisation (WHO) Fracture Risk Assessment tool (FRAX) is an algorithm able to give a 10-year probability of fracture risk using the WHO clinical risk factors, either alone or combined with a BMD T score [101]. WHO working group has identified several fracture-related risk factors other than low BMD, such as increasing age, female sex, smoke, personal history of fracture after age 50 years, parental history of hip fracture, low BMI, alcohol (> 3 units/day), corticosteroids use and other causes of secondary osteoporosis (eg, rheumatoid arthritis, thyroid disorders) [102]. Guidelines recommended treatment with antiresorptive drugs such as bisphosphonates and denosumab associated with calcium and vitamin D supplementation for prostate cancer patients receiving chronic endocrine treatment or cytotoxic agents with T-score < 2.5 and one or more risk factors [79].

Bisphosphonates (alendronate, pamidronate, zoledronic acid) have all been shown to prevent bone loss in prostate cancer patients treated with ADT, but 6-monthly denosumab (60 mg) are considered the most convenient and reliable treatments [103-107].

The HALT-prostate cancer trial, a randomized, phase III trial, randomized 1468 patients with nonmetastatic prostate cancer treated with ADT to receive denosumab (60 mg subcutaneously every 6 months) or placebo, associated with calcium and vitamin D [108]. The aim was to evaluate the role of denosumab in the prevention of bone loss. The primary endpoint was percent change of BMD in the lumbar spine after 24

months of treatment, the secondary endpoint was fracture rate. At 24 months, BMD of the lumbar spine had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group; significant differences between the two groups were seen at as early as 1 month and sustained through 36 months. Also secondary endpoint was met with a significant difference in vertebral fracture rate at 36 months in favor of denosumab (1.5% versus 3.9%) [78]. In the HALT study, the effectiveness of denosumab was also showed using serum bone turnover markers (BTM) [109], even if their use is not routine in clinical practice. BTMs were measured at baseline, month 1, and predose at months 6, 12, 24, and 36 in the overall population. In denosumab group, a rapid decrease of BTM values compared with placebo was recorded across patients subgroups, including men aged > 70 years, men with ADT duration at baseline. The effect of denosumab (60 mg subcutaneously) was compared also with alendronate (70 mg once weekly) in a multicenter, randomized, double-blind prospective 24-month observational study in prostate cancer patients treated with ADT [110]. Both denosumab and alendronate improved BMD, but denosumab increased BMD up to 5.6% at the lumbar spine after 24 months, while alendronate increased BMD by up to 1.1%.

Patients treated with denosumab experienced fewer vertebral fractures than those taking alendronate, although this difference was not significant [110]. A meta-analysis by Galvano et al. also studied the effect of denosumab on BMD and reduction of fracture risk with the placebo at 24 and 36 months, both in prostate and breast cancer patients. Denosumab showed a reduction of the BMD loss up to 36 months and a BMD increase both at 24 and 36 months. Patients taking denosumab had fewer vertebral and femoral fractures at 24 and 36 months. Denosumab did not increase toxicities compared to the placebo, nor in terms of SAEs risk (RR 1.06, 95% CI 0.98–1.15) and risk of “rebound effect” (RR 0.90, 95% CI 0.69–1.18) [112]. When looking to survival outcomes, both bisphosphonates and denosumab showed a potential benefit in prolonging survival when added to RADIUM-223 [112] in castration resistant prostate cancer. By the way, those observations should be considered as hypothesis-generating and not definitive.

Indeed, Denosumab (as Prolia®) was licensed in 2011 for treatment of osteoporosis both in postmenopausal women and in men at an increased risk of fractures, including as a result of CTIBL, as well as for the treatment of bone loss associated with hormone ablation in patients with breast or prostate cancer at increased risk of fractures [1].

The administration of denosumab is generally well tolerated with rare serious side effects as osteonecrosis of the jaw and hypocalcaemia. For this reason, the clinical monitoring of calcium levels is recommended to provide the adequate calcium and vitamin D supplementation during denosumab treatment.

Recently a panel of experts outlined recommendations on bone health management in prostate cancer patients treated with ADT. First, they advise to evaluate these patients, if possible, in a multidisciplinary group including oncologists, radiotherapists and urologists, rheumatologists, endocrinologists, geriatrics and orthopedics. Expert panels recommend to evaluate status of bone health at baseline and for the

duration of treatment, to perform DEXA scan, bone turnover markers, vitamin D, serum calcium and PTH at baseline and every 12-18 months afterwards. In the adjuvant setting, they suggest to reassess the fracture risk at the end of hormonal therapy: if the patient experienced no fracture during treatment, no particular monitoring will be necessary; otherwise, monitoring should be continued if the patient present any additional risk factor (e.g. new fracture) and therapy must be carried on [113].

Denosumab treatment on multiple myeloma and giant cell tumor of bone: a brief overview

Denosumab safety and efficacy has been explored in the '482 trial, published in 2018 [114]. In this international, phase III, randomized, double-blind trial 1178 patients affected by multiple myeloma were randomized to denosumab versus zoledronic acid to demostate non-inferiority of anti-RANKL therapy in preventing first SRE. Denosumab was confirmed to be effective as zoledronic acid with a comparable safety profile. This finding allowed FDA and EMA to approve subcutaneous denosumab at dosage of 120 mg every 4 weeks for patients affected by multiple myeloma.

Giant cell tumor of bone (GCTB) is a generally benign osteolytic tumor of the young age, more frequent diagnosed in female gender, associated with low risk of metastatization but frequent local recurrence [115-120]. Denosumab was employed both as adjuvant [121] and as upfront treatment for unresectable GCTB assuring tumor response in up to 90% of treated patients [122-123], testified by tissue giant cells disappearance, radiological tumor shrinkage surrounded by thicker calcium rim and subsequent significant pain reduction and functional preservation. Denosumab was tested also as pre-operative treatment for high risk planned surgery and provided a reduction in soft tissues infiltration together with lower surgical morbidity in up to 38% of patients [124-125].

Denosumab and cancer bone metastases

The introduction of denosumab has significantly improved therapeutic options for the prevention of SREs in in bone metastatic patients. Bone metastases are a consequence of a multifactorial and multi-step process in which bone microenvironment plays a crucial role in cancer cell colonization and growth. In particular, tumor cells deregulate bone homeostasis altering RANKL/OPG balance in favor of RANKL, leading to the loss of the skeleton integrity. Osteoclast activation, mediated by RANKL, induces the release of soluble factors that promote tumor cell growth resulting in a vicious cycle of tumor proliferation and bone destruction. Denosumab is able to inhibit osteoclast function and interrupt this vicious cycle blocking RANKL/RANK interaction [126-127].

Two large randomized trial demonstrated the superiority of denosumab compared to the zoledronic acid in reducing time to first and subsequent on-study SREs onset in bone metastatic breast cancer [69] and castration-resistant prostate cancer patients [128]. In another phase 3 trial, denosumab showed a non-

inferiority to zoledronic acid in delaying time to first SRE in patients with bone metastases from multiple myeloma or solid tumours other than breast or prostate [129]. A post hoc analysis of these three phase III trials confirmed that denosumab reduced the risk of first SRE compared to zoledronic acid [130].

However, international guidelines generally recommend the use of either denosumab or zoledronic acid in breast and prostate bone metastatic patients and in those with other solid tumors and high risk of SRE development [79-131].

5. Discontinuation of denosumab and rebound effect

The effect of bisphosphonates lasts for months or years after stopping treatment because these drugs have high affinity for binding hydroxyapatite [132].

In patients with postmenopausal osteoporosis, treatment with alendronate and zoledronic acid for 10 and 6 years respectively did not increase fracture risk. Patients that received treatment experienced a reduction of vertebral fracture after 5 years of alendronate and 3 years of zoledronic acid [133].

The prolonged use of bisphosphonate could cause side effects, such as atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ). Therefore, Guidelines support idea of a “drug holiday” after 3 years of treatment with intravenous zoledronic acid or 5 years with oral bisphosphonates for patients without a high fracture risk (e.g. older age, low hip T-score or high fracture risk score, previous fractures) [134-136]. This concept cannot be applied for drugs without skeletal retention, such as denosumab, because the fracture risk increases after their discontinuation [137-140]. Indeed, the optimal duration of treatment with denosumab is still controversial, because stopping denosumab therapy in osteoporotic patients is related to a “rebound phenomenon”, manifesting in an increased risk of multiple vertebral fractures associated with rapid bone loss [141].

While bisphosphonates remain in the skeleton long after their discontinuation leading to reduction of OC survival, [142] when denosumab treatment is stopped, a pool of OC precursors, quiescent during the therapy, become activated and probably a high RANKL / OPG ratio due to denosumab withdrawal leads to a rapid increase in bone turnover [143].

To our knowledge, there are evidence about this phenomenon in osteoporotic patients, but no data are reported for patients treated with denosumab for CTIBL.

In the FREEDOM Extension Trial the efficacy and tolerability of denosumab treatment for 10 years has been studied [144]. Denosumab confirmed its efficacy, but in patients who discontinued therapy, there was an increase of vertebral fracture rate with an odds of developing multiple vertebral fractures of 3.9 times higher in patients with prior vertebral fractures. The prolonged use of denosumab for 10 years did not increase frequency of side effects, nor the rate of AFF or ONJ [144].

In a small series of patients, women who stopped denosumab after 10 years, reported a rapid BMD loss at the total hip, often greater than what was gained during treatment [145]. Another case-control study also highlighted an increase in markers of OC formation and activity in patients who presented vertebral fractures after stopping denosumab [146].

In the FREEDOM trial, fracture incidence in patients who stopped denosumab and placebo was 9% and 7% respectively, after two years of therapy [147]. The rate of vertebral fractures was not higher in patients after stopping denosumab compared to the placebo group, but the follow-up was too short to validate this data. Several case reports have been reported in which multiple (≥ 2) vertebral fractures occurred within 2 to 10 months after denosumab cessation [145-146, 148-151]. Since there is no clear evidence of how long denosumab should be administered in this setting, European Calcified Tissues Society (ECTS) published a systematic review of the scientific literature and developed recommendations for managing patients [152]. According to ECTS recommendations, physicians should assess fracture risk after 5 years of treatment with denosumab. Patients at high risk should be treated with denosumab for 10 years or should switch to other therapy, while those at low risk should stop denosumab therapy and switch to an antiresorptive treatment (bisphosphonates, hormone therapy, or selective estrogen-receptor modulators) to prevent the “rebound effect”, without specifying which, in which dose, when or for how long. ECTS suggest that physician have to inform patients about benefit and risks of stopping denosumab treatment [152].

These recommendations apply to patients with osteoporosis and could also be valid for CTIBL because there are no specific recommendations for these patients. Studies on the duration of treatment with denosumab are necessary in cancer patients.

6. Safety and Economic Tolerability

Data from studies and clinical practice suggest an acceptable safety profile of long-term denosumab treatment.

The most severe side effects related to denosumab administration include ONJ, AFF and hypocalcemia. ONJ is characterised by painful bone destruction and delayed healing in the maxillofacial region more frequently in patients, with a recent history of tooth extractions, dental appliance or periodontal disease. ONJ incidence is usually more common (about 1%) when denosumab are administered on a monthly basis for control of metastases and much less frequent with 6-monthly use for prevention of bone loss.

In FREEDOM extension study enrolling postmenopausal women with osteoporosis undergone to 10 years of denosumab treatment, there were 13 adjudicated cases of ONJ (5.2 per 10,000 participant-years) [144]. No ONJ cases were noted with denosumab in the ABCSG-18 study using denosumab 60 mg every 6 months; by the contrast in D-CARE trial a higher proportion of patients in the denosumab group (120 mg every 3-4 weeks) developed ONJ [153]. Nevertheless, an oral examination, appropriate preventive dentistry and

good oral hygiene are strongly recommended before denosumab therapy as well as invasive dental procedures (extractions and implants) should be avoided during the treatment.

Similarly, the absolute risks of AFFs in patients treated with denosumab are low and appear to be more common in patients who have been exposed to long-term treatment. In the FREEDOM extension, only two patients with AFF were identified, and few case reports of AFF in patients treated with denosumab were documented [154-156]. Phase II and III clinical trials reported small asymptomatic reductions in serum calcium levels with corresponding increases of PTH levels [57,157]. The overall incidence of hypocalcaemia in ABCSG-18 study was approximate 0-2% compared to the higher incidence (7%) reported in D-CARE trial. In patients with renal impairments, hypoparathyroidism, malabsorption syndromes that are at high risk for hypocalcemia, the monitoring of serum calcium is warranted.

An advantage of denosumab over bisphosphonates, is that it is relatively safe in patients with impaired renal function and it should be preferred in such situations.

The improvement of osteoporosis medication adherence can reduce osteoporosis-related health care costs by avoiding fractures. Despite the high social and economic cost of osteoporosis, efforts to improve the detection, diagnosis, and treatment of osteoporosis are necessary to reduce the growing clinical, economic, and societal burden. Different studies demonstrated that anti-osteoporosis medications significantly reduced vertebral and nonvertebral fractures incidence. Economic analyses, based on efficacy estimates, showed that these medications are cost-effective for both primary and secondary prevention [158-159].

Bilezikian et al showed how long-term treatment with denosumab decreased upper limb fracture risk and increased forearm BMD in osteoporotic patients, suggesting beneficial effects on both cortical and trabecular bone accruing over time [160]. The potential health economic benefits of treatment must be taken into account.

Another study demonstrated that nonadherence medications result in around a 50% reduction in the potential benefits and a doubling of the cost per quality-adjusted life-year gained from these medications [161].

Persistent pharmacotherapy is recommended to prevent osteoporotic fractures and reduce health care costs in osteoporotic patients, included patients with chemotherapy-induced osteoporosis and bone metastasis [162]

7. Conclusions

Preserving bone health, especially in patients with prostate and breast cancer, must be a clinical goal to preserve the quality of life of our patients. The use of denosumab with a six-monthly schedule has been shown to reduce the time to the first fracture, increase BMD and promising survival results.

Based on these results, scientific societies and expert panels report the adjuvant denosumab in this setting of patients as an effective and safe drug.

Expert Opinion

The improved survival of cancer patients highlighted the issue of bone health, which remains an unfulfilled clinical need because not yet receiving the right attention of the scientific community. The causes of bone loss in cancer patients and the subsequent functional consequences are multifactorial. Anti-tumoral treatment side effects together with preexisting clinical risk factors for fracture (such as, advanced age, use of glucocorticoids, a history of smoking, low body mass index, a family or personal history of fragility fracture or osteopenia at basal) are well recognized risk factors.

Anticancer treatment induced bone loss increases fracture risk and may require use of a bone targeted agent in addition to lifestyle modifications: weight-bearing exercise, smoking cessation, reduced alcohol intake and vitamin D supplements should be encouraged.

Clinicians need to recognize that multidisciplinary treatments are available to reduce skeletal morbidity from metastatic disease and the strategies required to minimise cancer treatment induced damage to the normal skeleton. Moreover, clinicians should be aware of how important is the early assessment of bone loss risk when anticancer treatment is planned in order to plan effective prevention strategy.

In at-risk patients, the evaluation of clinical risk factors and measurement of BMD by dual X-ray absorptiometry (DXA) is recommended. Vitamin D and Calcium supplementation are well-known first-level strategy in fractures prevention. The efficacy of different bisphosphonates have been tested in several clinical trials in both breast and prostate cancer but the comparative efficacy of different drugs remains uncertainty.

Treatment with denosumab at dosage of 60 mg subcutaneously every 6 months has been proposed: for postmenopausal women and men with osteoporosis, for breast cancer patients during adjuvant AI therapy and in prostate cancer patients treated with ADT.

In patients with breast and prostate cancer at an increased risk of fractures, the use of denosumab reduce the time to the first fracture, increase bone mineral density and promising survival results. Denosumab is generally well tolerated with rare serious side effects as osteonecrosis of the jaw and hypocalcaemia. For this reason, the clinical monitoring of calcium levels is recommended to provide the adequate calcium and vitamin D supplementation during treatment.

Even if Denosumab did not increase toxicities, nor in terms of SAEs risk, but the duration of treatment remains controversial, mainly due to the rebound effect.

Many questions remain unanswered: how select cancer patients; what regimen; what treatment duration; how to continue the follow-up after therapy discontinuation; how to repair damaged bone-tissue when matrix turnover is effectively stopped by antiresorptive agents. Specific populations of utmost relevance, such as premenopausal breast cancer patients still do not receive the appropriate bone preserving

medications, which are clearly able to slow down the bone loss associated with subsequent osteoporosis. Taking into account the economic consequences for public health systems, preventing the long-term morbidity derived from anti-cancer treatments is of the utmost importance in order to reduce late impairments in cancer survivors. Preclinical and clinical data are still lacking on that issue. Design of randomized clinical trials is mandatory to give answers to clinicians about the best strategy to prevent and recover bone loss, osteoporosis and long-term consequences from anticancer therapies.

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FIGURE 1: Schematic representation of bone health actors' cross-talk.

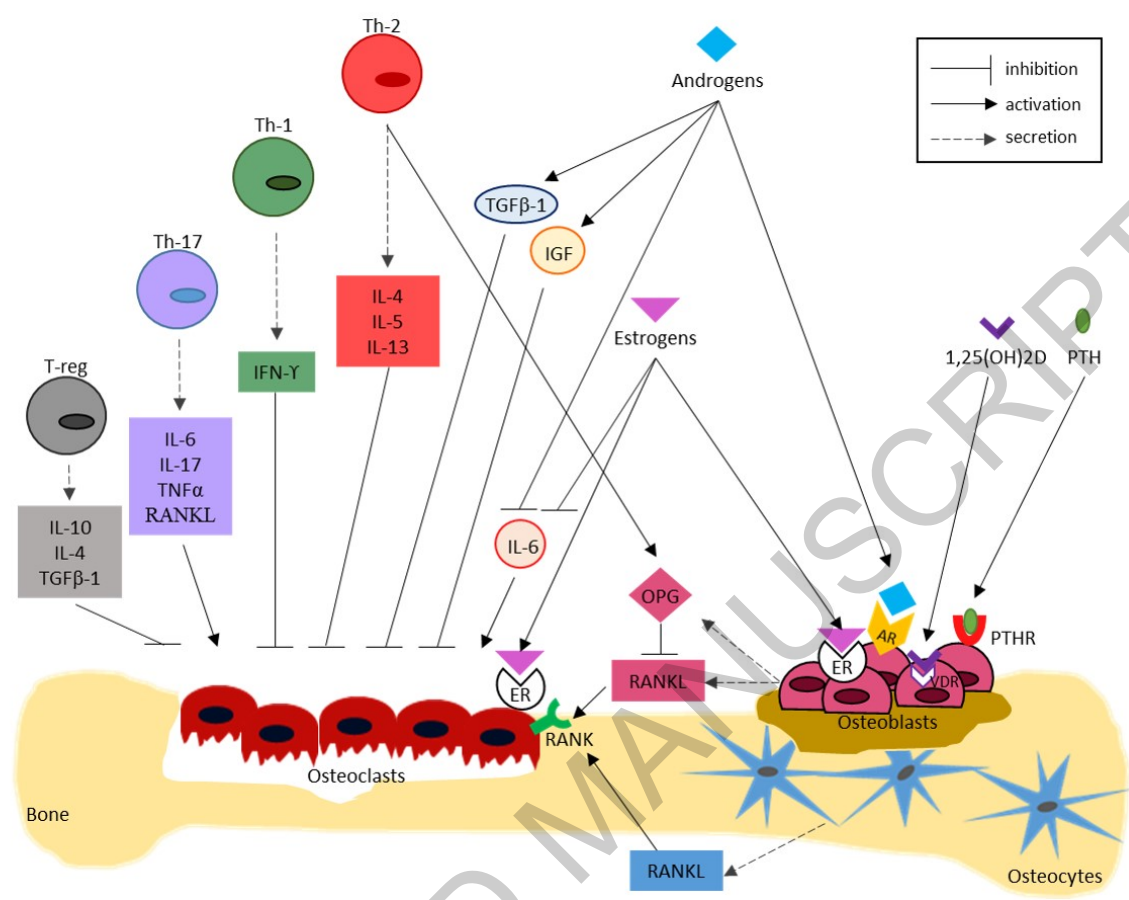


Table 1: Clinical trial investigating the effects of chemotherapies, hormone therapies and denosumab on bone health in breast cancer patients

Setting	N° of patients	Treatment	Results	References
Premenopausal	49	Chemotherapy	Decrease of BMD in the spine in patients having ovarian failure	[70]
Pre and Postmenopausal	492	Chemotherapy	Higher BMD loss in the spine in premenopausal vs postmenopausal patients	[73]
Postmenopausal	130	Chemotherapy	Lower BMD in chemotherapy treated patients	[74]
Postmenopausal	4115	Als vs Tamoxifene vs Chemotherapy	Only AI therapy was associated with a higher incidence of fractures	[75]
Postmenopausal	9366	Anastrozole vs Tamoxifene	Higher fracture rates in patients receiving anastrozole	[83]
Postmenopausal	252	Als +/- Denosumab	Denosumab increased BMD lumbar spine	[84]
Postmenopausal	3420	Als +/- Denosumab	Denosumab delayed time to first clinical fracture	[55]

Als= aromatase inhibitors