Breast Cancer: Targets and Therapy

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REVIEW

Cancer Treatment-Induced Bone Loss: Role of Denosumab in Non-Metastatic Breast Cancer

Boman Dhabhar

Department of Medical Oncology, Fortis Hospital, Mumbai, India

Correspondence: Boman Dhabhar, Consultant, Medical Oncology, Fortis Hospital, Mulund, Mumbai, 400078, Maharashtra, India, Email drboman@hotmail.com

Abstract: Chemotherapeutic agents, endocrine therapy and radiotherapy used in the management of breast cancer are known to cause decreased bone mineral density, and thus, increased incidence of fractures. A majority (~60%) of the breast cancer patients in India are either estrogen (ER) or progesterone hormone receptor (PR) positive. Adjuvant treatment with aromatase inhibitors (AIs) is the treatment mainstay for hormone-sensitive disease in postmenopausal (PM) women, with reduced bone mineral density (BMD), which results in increased fracture rates. Zoledronic acid, alendronate, risedronate and denosumab have been the agents of choice for managing bone loss. Denosumab 60 mg is approved for gaining bone mass in women with breast cancer who are at high risk for fracture following adjuvant AI treatment. The phase III HALT-BC data indicate an improvement in BMD with denosumab and a 50% reduction in clinical fractures, with significant improvements seen at the lumbar spine, distal third of the radius, and total hip. Denosumab has several advantages over other bone modifying agents such as subcutaneous self-administration by the patient themselves, no requirement of hospitalization, no dose modifications in renal impairment, and low incidence of acute phase anaphylactic reactions. We review the available evidence of denosumab for managing bone loss in non-metastatic breast cancer patients.

Keywords: nonmetastatic breast cancer, postmenopausal women, denosumab, bone loss, bone mineral density, fracture

Introduction

Globally, breast cancer is one of the most commonly diagnosed cancer, and the leading cause of mortality in women with cancer.[1,2] Of all the cancer cases worldwide, 11.7% cases are breast cancer, of which 2,261,419 cases are newly diagnosed and 684,996 (6.9%) deaths reported, as per GLOBOCAN 2020.[3] In India, the incidence of breast cancer was 26.3% (178,361 cases) in 2020, which is highest among all other cancers in women.[4]

Postmenopausal (PM) breast cancer accounts for ~80% of all newly diagnosed breast cancers.[5] Approximately 75–80% of the breast cancer cases are hormone-receptor (HR; either estrogen [ER] or progesterone [PR]) positive.[6,7] In India, 50–60% of breast cancer patients are HR-positive.[8–10] The American Society of Clinical Oncology and the European Society of Medical Oncology guidelines recommend oophorectomy or adjuvant therapy with endocrine agents in HR-positive disease to prevent recurrence or developing new breast cancer. These include selective ER modulators (SERMs), agonists for luteinizing hormone (LH)-releasing hormone (LHRH) and aromatase inhibitors (AIs).[6,11–13] The extensive use of adjuvant endocrine treatment has led to reduced mortality in HR-positive early breast cancer (EBC).[7]

There is an increased risk of breast cancer occurrence in individuals with advanced age, particularly after 60 years,[14] who also have a high risk of developing osteoporosis. There is also a high risk of osteoporosis in breast cancer patients with low estrogen levels. Low estrogen levels cause an increased rate of bone resorption leading to decreased levels of bone mineral density (BMD), resulting in osteoporosis and increased fracture risk.[6,15,16]

Bone Loss in Breast Cancer

In the healthy state, osteoblast-led bone formation and osteoclast-led resorption of bone are balanced,[17] but in breast cancer, there is an increased osteoclastic activity attributable to the raised transforming growth factor, cytokine, parathyroid hormone-related protein, tumor necrosis factor, insulin-like growth factor 1, and interleukin (IL)-1 and 6

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levels.[18,19] The increased risk of osteoporosis and fractures is observed in breast cancer patients with advanced age (>60 years), and low estrogen levels due to hormonal treatment or loss of ovarian function, especially in premenopausal women, due to several medications or surgical interventions.[6,14–16,20]

In PM women, a decreased bone density is observed due to natural physiological decline in estrogen levels.[21] The Women's Health Initiative evaluated the incidence of fractures before and after cancer diagnosis in 146,959 PM women who did not have cancer history at baseline. A 9-year follow-up data reported a 55% higher fracture risk in women after diagnosis of breast cancer vs women who remained cancer-free.[5] Furthermore, chemotherapy, radiotherapy, endocrine therapy, and several other medications such as glucocorticoids have been linked with bone loss in PM breast cancer patients.[16,22]

Hormonal (Endocrine) and Anti-Estrogen Therapy-Induced Bone Loss

Gonadotropin-releasing hormone (GnRH) agonists decrease estrogen production in pre- or peri-menopausal women.[23] The ovarian suppression due to GnRH agonists (leuprolide, nafarelin, goserelin) reduces circulating estrogen leading to accelerated bone resorption and decreased BMD (~5%).[22,24] Tamoxifen is a SERM anti-estrogen agent, which has been the cornerstone for managing the HR-positive disease, but a meta-analysis in PM women (n = 31,920) demonstrated that adjuvant AIs were superior over tamoxifen with 30% more reduction in the recurrence rate in ER-positive EBC.[25]

AI Therapy: Bone Loss and Fracture Risk

The AIs are being used as a part of the treatment mainstay in PM women with hormone-sensitive EBC.[11] The AI use has demonstrated a 2- to 4-times greater decrease in the BMD as compared with physiologic postmenopausal BMD loss.[26] Several phase III randomized studies have reported a loss of up to 2.6% BMD in PM breast cancer patients within the first year of AI treatment (Figure 1).[27–31] In ATAC trial in PM women with EBC, the median percent change from baseline in BMD at 5-years with adjuvant anastrozole vs tamoxifen vs control (breast cancer women not receiving any treatment post-primary surgery) group were −6.08% vs +2.77% vs +1.35%, respectively, at the lumbar spine, and −7.24% vs +0.74% vs −2.81%, respectively, at the total hip.[32]

There is a high fracture risk in women receiving treatment with AI agents due to decreased estradiol in plasma as a result of blocking the activity of aromatase enzyme predominantly in the adipose tissues.[22,33] Mincey et al identified 1354 patients receiving an AI and 11,014 controls via medical and pharmacy databases in a large managed care population and reported that the fracture rate was higher in patients receiving AIs vs controls (13.5% vs 10.3%, P = 0.001); the AI group had a 40% more risk of fractures. The incidence rate of fracture per 100 person-years was 35% higher for the AI group (incidence rate

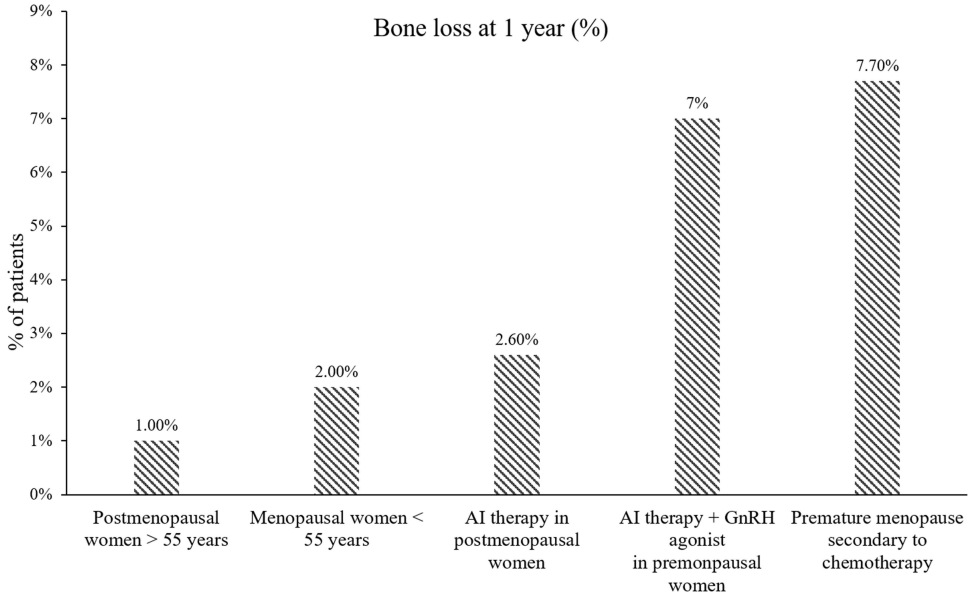

Figure 1 Bone loss in women at 1 year. Data from [27–31].

per 100 person-years: 8.6 for AI vs 6.36 for control groups).[34] Overall, the AI-associated bone loss was ≥2-fold higher vs healthy, age-matched, PM women, leading to significantly higher fracture rates regardless of the AI agent used.[35]

Chemotherapy and Bone Loss

Adjuvant chemotherapy increases the loss of bone mass in patients with breast cancer. Burning et al reported that adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) led to premature ovarian failure in 71% of premenopausal women and had a significantly decreased BMD (1.17 g/cm^2 vs 1.29 g/cm^2) vs the controls (women pair-matched for age and year of breast cancer surgery who did not receive chemotherapy).[36] Bines et al reported the average chemotherapy-related amenorrhea rate at 68% in premenopausal breast cancer patients who were administered chemotherapy with adjuvant CMF.[37] The ovarian failure due to chemotherapy led to rapid bone loss in the lumbar spine (9.5%) and femoral neck (4.6%) within 2 years in premenopausal breast cancer patients.[38]

Greep et al reported a significantly lower bone density at hips and spine in PM EBC patients receiving adjuvant chemotherapy vs patients who did not receive adjuvant chemotherapy.[39] In addition to an increase in the osteoclastic activity observed in breast cancer, increased bone resorption has been reported with several agents including taxanes, methotrexate, doxorubicin, cyclophosphamide, 5-fluorouracil and cisplatin.[16]

Radiotherapy Induced Loss in Bone Mass

The use of radiotherapy in women with breast cancer can have adverse effects on bones[40] with fractures reported.[41–45] Though the precise mechanism of radiotherapy-induced loss in bone mass is uncertain, it is believed that radiotherapy through mechanisms of cell cycle arrest, altered differentiation, and increased apoptosis decrease active osteoblasts.[46] The use of radiotherapy for cervical, endometrial, and vaginal cancers has been associated with significant decrease in BMD.[44] In a study by Dybvik et al, 3% of women with breast cancer treated with breast radiotherapy required total hip replacement at 8 years.[45]

Treatment for Loss of Bone Mass

To reduce the risk of fractures in cancer patients with non-metastatic disease and osteoporosis, treatment with bone-modifying agents (BMAs) may be offered as per the European Society of Medical Oncology (ESMO) guidelines.[26] The BMAs include intravenous (IV) or oral bisphosphonates and denosumab.[26] In addition, lifestyle interventions, exercise, optimized dietary vitamin D and calcium intake along with other pharmacological interventions are recommended.[26,47] Several antiresorptive agents have emerged, which can reduce bone loss in patients with osteoporosis through inhibition of bone degeneration and/or acceleration of bone formation. The antiresorptive agents include bisphosphonates (alendronate, etidronate, ibandronate, risedronate, zoledronate), SERMs (tamoxifen, raloxifene) and hormonal (estrogens) agents.[25,48,49]

In 2010, the US Food and Drug Administration (FDA) has approved denosumab, an inhibitor of the receptor activator of nuclear factor-kappa-B (RANK)-ligand (RANKL).[50] As per the American Society of Clinical Oncology (ASCO) guidelines, oral or IV bisphosphonates and subcutaneous denosumab are efficacious options in this patient population.[26]

Denosumab Prevents Bone Loss: Mechanism of Action

The RANKL is an essential mediator in bone destruction. Decreased estrogen levels cause an increased RANKL secretion with a simultaneous decrease in osteoprotegerin expression, thus, causing an increase in the osteoclast activity leading to reduction in the bone mass.[16] Denosumab inhibits the RANKL activity through binding with high specificity and affinity, resulting in diminished osteoclast recruitment, maturation and action, thus slowing down bone resorption.

What Do Guidelines Say?

As per the 2011 practical guidance by Hadji et al, intravenous zoledronic acid is a recommended agent, but denosumab and oral bisphosphonates could be considered in individual patients, for managing bone loss caused due to AI therapy in PM breast cancer patients. In 2017, an update of the practical guidance by Hadji et al included the use of denosumab

along with bisphosphonates for the prevention of bone loss in breast cancer patients due to AI therapy.[51] The 2019 ASCO guidelines recommend use of BMAs, including denosumab, for nonmetastatic cancer patients with osteoporosis or who are at increased fracture risk.[26] As per the 2020 ESMO clinical practice guideline, denosumab is recommended as the choice of treatment for the prevention of fractures in postmenopausal women with EBC.[52] However, the 2019 St. Gallen consensus guidelines recommended bisphosphonate use in postmenopausal women with breast cancer, and substituting denosumab for bisphosphonates was not recommended.[53]

Subcutaneous denosumab 60 mg 6 monthly is approved for the management of PM women with osteoporosis at high risk for fracture, women with glucocorticoid-induced osteoporosis at high risk for fracture and increased bone mass in women at high risk for fracture receiving adjuvant AI therapy for breast cancer.[50] We review the available evidence of denosumab administered at a dose of 60 mg as 6 monthly injections to manage the loss of bone mass in non-metastatic breast cancer (non-MBC) patients.

Denosumab for the Treatment of Bone Loss in PM Women with Low BMD

Denosumab reduces bone turnover markers and causes a rapid and sustainable increase in BMD in PM women with low BMD.[54] The long-term 10 years data of the FREEDOM trial and its 7-year open-label extension demonstrated that denosumab increased the BMD and decreased the risk of vertebral, nonvertebral and hip fractures in PM women with osteoporosis or low BMD.[55,56]

Denosumab in EBC Patients Receiving Adjuvant AI Therapy: Phase III Study

A phase III Hormone Ablation Bone Loss Trial in Breast Cancer (HALT-BC) trial in HR-positive non-MBC patients receiving placebo (n = 122) or subcutaneous 6-monthly denosumab 60 mg (n = 123) (Figure 2) for AI–induced bone loss demonstrated that BMD at lumbar spine significantly ($P < 0.0001$) increased with denosumab treatment after 12 (+5.5%) and 24 months (+7.6%) compared with placebo.[57] Lumbar spine BMD showed significant changes as early as 1 month with denosumab. These effects on BMD were independent of the AI duration before denosumab administration, the previous AI administered, or whether the patients had received tamoxifen previously, suggesting that denosumab was beneficial in these patient populations. Furthermore, there were no vertebral fractures reported whereas 6% of patients in each group had nonvertebral fractures.[57] A post hoc analysis to demonstrate the treatment effects on the preservation of BMD at 24 months showed >3% increase in the BMD at the lumbar spine in 80% patients receiving denosumab vs 13% patients receiving placebo; >6% increased BMD at the lumbar spine was seen in 50% patients receiving denosumab vs 3% receiving placebo. Denosumab showed increased BMD vs placebo at other sites after 2 years – total hip (4.7%), femoral neck (3.6%), and distal third of the radius (6.1%).[57]

Also, denosumab caused a rapid reduction in bone remodeling markers with 63% to 80% reductions in serum collagen type I cross-linked C-telopeptide (sCTx) levels and 71% to 73% reductions in procollagen I intact N-terminal

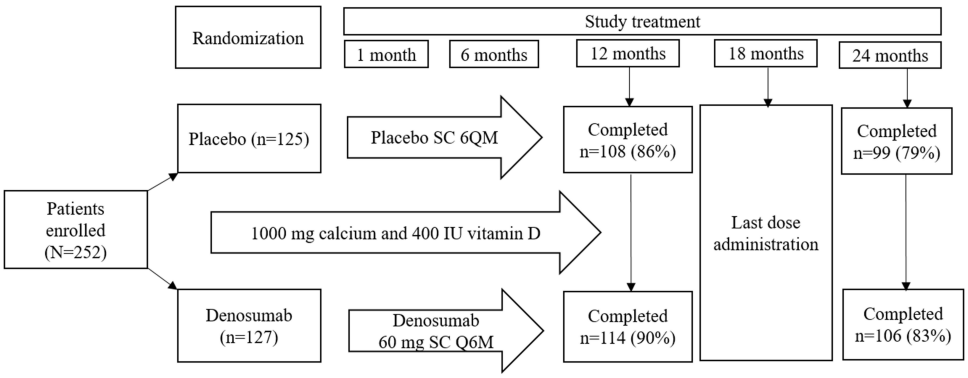

Figure 2 Study design: denosumab vs placebo in women receiving AI-therapy for breast cancer in phase III study by Ellis et al. Data from Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol. 2008;26(30):4875–4882. doi:10.1200/JCO.2008.16.3832.[57]

(PINP) levels over 6 to 24 months during the study. The safety profile was comparable between denosumab and placebo groups.[57] The authors concluded that 6-monthly administration of denosumab led to a significant improvement in the BMD along with reduced bone turnover over 24 months, with similar rates of AEs vs placebo.[57]

ABCSG-18 Trial

The ABCSG-18 trial studied the effects of 6-monthly denosumab 60 mg (n = 1711) or placebo (n = 1709) in HR-positive PM breast cancer patients receiving adjuvant AIs and showed that denosumab led to a 50% greater reduction in the risk of clinical fractures (hazards ratio: 0.50, 95% CI: 0.39–0.65; P < 0.0001) vs placebo. The losses in BMD at 36 months for denosumab vs placebo at the lumbar spine were 10% vs 74%, at the femoral neck were 22% vs 75% and at the total hip were 17% vs 78%. Furthermore, denosumab showed significantly greater (P < 0.0001) improvements in BMD vs placebo throughout the study (Figure 3). The authors concluded that denosumab had significantly improved BMD and reduced fractures, which was independent of baseline BMD (T-score), age, HR receptor status and whether the patient had previously received AI or not.[58]

In a subsequent analysis of the ABSCG-18 trial, denosumab showed improved disease-free survival (DFS) vs placebo (14% vs 16.8%). The univariate analysis showed that denosumab significantly improved DFS in PM patients aged <60 years with ER and PR double-positive status (HR, 0.81 [0.67–0.98]) as compared with placebo. Overall, the researchers concluded that adjuvant denosumab was an effective treatment option irrespective of the baseline BMD status in PM women with HR +ve EBC.[59]

Evidence from Asian Studies

In a phase II study, Nakatsukasa et al evaluated the effects of SC denosumab 60 mg given every 6 months on the BMD of lumbar spine and femoral necks in Japanese PM women (n = 100) with HR-positive postoperative breast cancer, who had low BMD (T-score −1.0 to −2.5) and who were scheduled or receiving AI treatment along with calcium and vitamin supplementation. Improvements in the BMD for the lumbar spine (4.7%), right femoral neck (2.4%), and left femoral neck (1.4%) were observed at 1 year. These improvements in BMD were independent of whether the patients received prior AI therapy or not. Furthermore, there were no incidences of non-traumatic fractures at 12 months in patients who received AI treatment and denosumab.[60]

Denosumab treatment led to quick decreases in bone remodeling marker levels (tartrate-resistant acid phosphatase 5b [TRAP5b; 59.2%] and bone alkaline phosphatase [BAP; 52.2%]) at 1 year.[60] A subgroup analysis based on the risk factors for bone loss showed that BMI (<25, ≥25 kg/m^2), time since menopause (≤5, >5 years), age (<65, ≥65 years), and

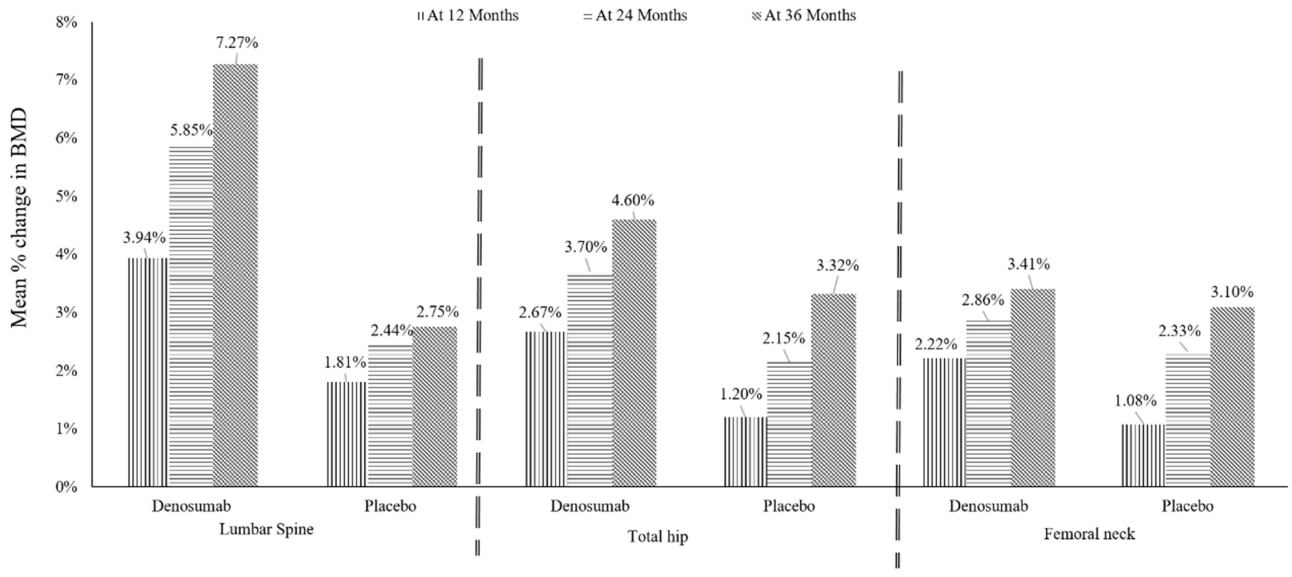

Figure 3 Mean % changes in BMD at total lumbar spine, total hip, and femoral neck for denosumab versus placebo at 12, 24, and 36 months.

baseline BMD T-score for right and left femoral necks (≤ −1.0, > −1.0) did not affect BMD when compared with previous AI therapy (before or with).[61]

In a 12-month, nonrandomized, prospective study, Nakatsukasa et al evaluated SC 6-monthly denosumab 60 mg in Japanese PM HR-positive breast cancer patients (n = 102) with osteoporosis (T-score ≤ −2.5) who received adjuvant AI therapy. Approximately 58% of patients had initiated AI therapy before denosumab. The increases in BMD were 6.6% (95% CI: 5.7–7.6) for the lumbar spine, 3.3% (95% CI: 2.2–4.4) for the right femoral neck and 4.1% (95% CI: 2.7–5.5) for the left femoral neck. These improvements in the BMD were regardless of the previous AI therapy history. Also, no incidences of non-traumatic fractures were reported in patients who received AI treatment and denosumab. Reductions were observed with denosumab treatment in TRAP5b (59.5%) and BAP (49.8%) markers at 12 months.[62] In the 24-month follow-up of this study, denosumab treatment led to BMD improvements at the lumbar spine (7.0% [95% CI: 5.9–8.0]), right femoral neck (3.4% [95% CI: 2.4–4.5]) and the left femoral neck (3.6% [95% CI: 2.6–4.6]). There were no clinical fractures reported in patients receiving AI and denosumab.[63]

Studies have evaluated the use of denosumab administration in patients currently receiving AI therapy or who had received AI therapy. There is little evidence suggesting the optimal time to initiate treatment with denosumab. From a retrospective case-control study in BC patients who received AI therapy categorized as ≤12 or >12 months of AI treatment, Scaturro et al concluded that early treatment with denosumab as compared to a delayed treatment might result in the prevention of incident fragility fractures of vertebra and hip, and a higher improvement in the lumbar spine and femoral neck T-scores.[64]

Denosumab vs Zoledronic Acid

For IV zoledronic acid treatment, patients are required to visit hospitals every few months (3–12 months), which causes an additional burden related to transport, time for waiting, set up, 15-min infusion and monitoring.[65,66] Furthermore, intravenous administration, monitoring of renal functions with required dose modifications, and acute-phase anaphylaxis reactions are a few other challenges with zoledronic acid treatment.[65–67] Denosumab therapy overcomes these limitations as it is given subcutaneously, the patient can self-administer, thus improving the compliance, and it does not require hospitalization, has a lesser incidence of acute phase anaphylaxis reactions, while monitoring of renal functions and subsequent dose changes are not warranted.[52,67–69]

A head-to-head comparison on the efficacy and safety of denosumab vs zoledronic acid in PM women with breast cancer is not available but denosumab has demonstrated a delayed time for developing skeletal-related events as compared with zoledronic acid in cancer patients with bone metastasis.[70]

Mixed Treatment Meta-Analysis – Prevention of Fractures

Denosumab was compared with zoledronic acid for preventing fractures in PM EBC patients receiving AIs in a mixed treatment meta-analysis from five phase III studies (2 studies for denosumab and 3 studies for zoledronic acid; n = 5545). The risk of fractures was not different between immediate treatment (denosumab or zoledronic acid) vs delayed treatment (odds ratio [OR]: 0.78 and 0.88; respectively) at 12 months cut-off; however, it was reduced for immediate denosumab compared to delayed treatment which was not observed between immediate zoledronic acid vs delayed treatment (OR: 0.50 and 0.91; respectively) at the 36 months cut-off.[71]

Denosumab vs Other Bone Modifying Agents (BMA) in Breast Cancer

A recent meta-analysis (n = 7699) compared different BMAs (denosumab: n = 1838, risedronate: n = 312, zoledronate: n = 1708, and no upfront treatment: n = 3841). The analysis reported that denosumab and zoledronate showed significantly increased BMD vs risedronate or no treatment groups at the lumbar spine and total hip at 12 and 24 months (Figure 4). Denosumab led to a significant increase in BMDs at the total hip at 24 months vs zoledronate (0.66%).[72] The authors of the network meta-analysis concluded that denosumab treatment also led to an increase in the BMD in the cortical-bone-rich hip, along with significantly decreased risk of fracture.[72]

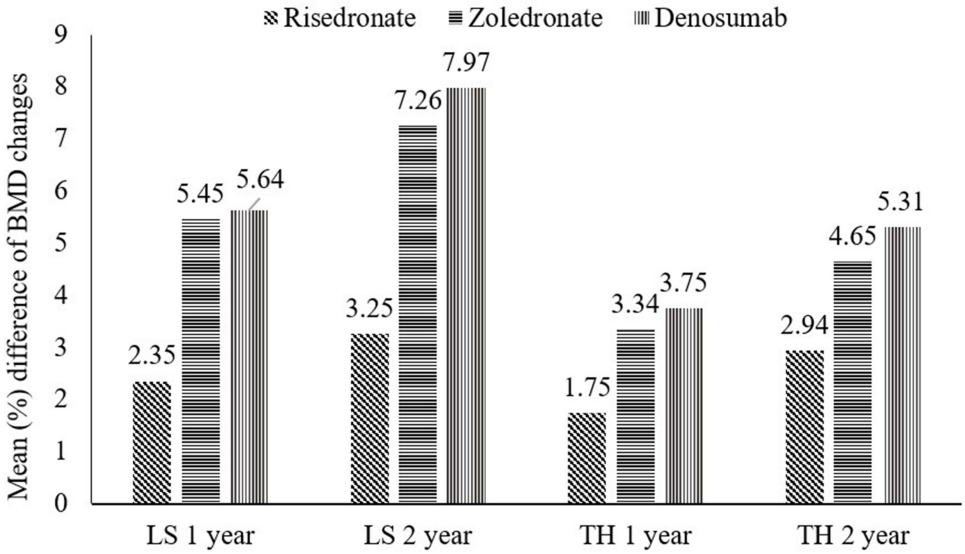

Figure 4 Mean difference (95% CI) of BMD changes with each treatment compared with no upfront treatment.
Abbreviations: BMD, bone mineral density; LS, lumbar spine; TH, total hip.

Safety in Non-MBC Patients Receiving Adjuvant AI Therapy

The use of denosumab is contraindicated in patients with hypocalcemia and women of reproductive potential/pregnancy. The AEs of clinical interest with denosumab administration include osteonecrosis of the jaw (ONJ), hypocalcemia, multiple vertebral fractures after treatment stoppage, atypical femoral fractures, musculoskeletal pain, infections, skin reactions, and suppression of bone turnover. The AEs reported in the clinical studies of denosumab in PM women with breast cancer are back pain, musculoskeletal pain, hypercholesterolemia, pain in extremity, fatigue, cystitis, and arthralgia.[50,57,58,60,62,63,73] Furthermore, there were no reports of ONJ, hypocalcemia, or non-traumatic fractures in these clinical studies.[50,57,58,60,62,63] Table 1 enlists AEs with denosumab in non-metastatic breast cancer patients reported in clinical studies.

The ONJ is a rare but serious complication in PM women receiving bisphosphonates or denosumab. A systemic review of 3 randomized phase III studies demonstrated no significant (P = 0.11) difference in the incidence of ONJ between denosumab (52 ONJ cases in 2841 patients) and zoledronic acid (37 ONJ cases in 2836 patients).[74] Overall, ONJ incidence in clinical studies in patients with cancer ranges from 0.7% to 6.7% with bisphosphonates[75] whereas it is 1.7% with denosumab.[76] Furthermore, a dental evaluation and suitable prophylactic dental measures are recommended before initiating denosumab therapy.[50] The increased multiple vertebral fracture risks after stoppage of denosumab

Table 1 AEs with Denosumab Treatment in Clinical Studies in Non-Metastatic Breast Cancer Patients

AE	ABCSG-18 Trial [47] %	Ellis et al,[57] %	Asian Study in Patients with T Score −1.0 to −2.5 [49] %	Asian Study in Patients with T Score <−2.5 [52] %
Arthralgia	26	24	19.4	37.6
Pain in extremity	6	14.7	10.7	25.8
Back pain	9	14	9.7	15.1
Fatigue	6	13.2	-	-
Constipation	-	11.6	-	-
Cough	-	10.1	-	-
Insomnia	-	9.3	-	-

Abbreviation: AE, adverse event.

remain a concern,[73,77] and use of a bisphosphonate agent after stopping denosumab is recommended by the European Calcified Tissue Society to decrease this risk.[78]

Denosumab: Dosage, Administration and Usage

Denosumab is supplied as a prefilled syringe (60 mg in 1 mL clear, colorless to pale yellow solution) and should be administered as a subcutaneous injection every 6 months. Denosumab should be removed from the refrigerator 15–30 minutes before administration. Once the drug is administered, a green safety guard which is present on the syringe needs to be manually slide over the needle and locked securely in place to minimize accidental needle sticks. However, caution is required that the green safety guard should be activated only after administration as if done before drug administration, it will lock and avert injection.[50]

Denosumab Cost-Effectiveness

Financial constraints preclude many eligible patients from receiving appropriate treatment, particularly uninsured patients and in countries where health insurance is not common. The cost-effectiveness of denosumab versus bisphosphonates evaluated for the treatment of bone metastases from solid tumors by Ford et al concluded that denosumab was found to be cost-effective as compared with zoledronic acid but only with patient access scheme.[79] Several biosimilars of denosumab are being developed to provide a cost-effective alternative to Prolia® (innovator denosumab manufactured by Amgen, USA).[80] In India, biosimilar denosumab is approved and may provide a cost-effective alternative to Indian patients.

Summary

Bone loss and fractures are common complications of treatments used in breast cancer patients. Aromatase inhibitors are the standard of care for hormone receptor-positive early breast cancer, which are known to decrease the BMD and increase the risk of fractures. Bisphosphonates and denosumab are established agents in the management of bone health in cancer patients. Studies have confirmed that denosumab prevents loss of bone mass in HR-positive EBC patients. Denosumab prevents loss of bone mass, maintains bone mineral density, and reduces fracture risk. Denosumab 60 mg SC 6-monthly is recommended in women at high risk of fractures receiving adjuvant AI treatment for breast cancer. The availability of biosimilar denosumab in India may provide an alternative cost-effective option for these patients.

Key Clinical Takeaways

- The use of hormonal therapy with adjuvant aromatase inhibitors (AI) increases the risk of bone loss and fractures in breast cancer patients.
- The agents of choice for managing bone loss and preventing fracture include zoledronic acid, alendronate, risedronate and denosumab.
- Denosumab (60 mg subcutaneous 6 monthly injections) is recommended for improving bone mass in women with breast cancer who receive adjuvant AI treatment and are at a high risk of fractures.
- Denosumab has certain advantages over bisphosphonates that include no requirement of renal monitoring and dose modification in renally impaired patients, ease of self-administration (subcutaneous), and a tolerable safety profile.
- Denosumab is not recommended in pregnancy and patients with hypocalcemia.
- Due to the risk of hypocalcemia worsening, calcium and minerals (magnesium and phosphorus) should be monitored for 14 days after denosumab administration.
- Serial dental examinations are suggested with suitable precautionary dentistry measures to avoid osteonecrosis of the jaw (ONJ).
- When denosumab is planned to be stopped, a rapid transition to an alternative antiresorptive agent should be advocated to avoid the undue fracture risk.

Author Contributions

The author has made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The author reports no conflicts of interest in this work.

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