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Denosumab for the Prevention of Skeletal-Related Events in Breast Cancer Bone Metastasis: A Literature Review

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Abstract

Background: *Breast cancer is the leading cause of cancer-related mortality among women worldwide, with more than 90% of these deaths attributed to metastases [1]. Among patients with metastatic breast cancer, approximately 65% to 75% develop bone metastases [1,2].These metastases are responsible for serious skeletal-related events (pain, pathological fractures, spinal cord compression, hypercalcaemia). RANKL inhibitors, particularly denosumab (Xgeva®), represent a major therapeutic option in preventing bone complications related to these metastases. We therefore aim to conduct a literature review to evaluate the efficacy and safety of denosumab (Xgeva®) in the prevention of skeletal complications in patients with breast cancer and bone metastases.*

Methods: *A literature review was conducted using PubMed and MEDLINE databases from 2014 to 2025. The keywords used were « breast cancer », « denosumab » and « bone metastases ». A total of 140 articles were initially identified. After screening the abstracts, 31 articles were selected for full-text review, and 20 were finally included in the analysis.*

Results /Discussion: *This review demonstrated that denosumab (Xgeva®) significantly delays the onset of the first skeletal-related event in patients with breast cancer and bone metastases, reducing the risk by 14% to 24%[3–6]. Denosumab also significantly lowers the incidence of fractures in both premenopausal and postmenopausal women[3,7,8]. Compared to zoledronic acid, it reduces this risk by 23%[9] . Regarding bone pain, treatment with denosumab significantly delays the onset or worsening of pain in patients with moderate to severe pain[4,10,11], with a 17% risk reduction (p = 0.003)[10] . Denosumab also appears to*

reduce the risk of spinal cord compression [4,8,13] . According to Charles L., the probability of spinal cord compression under denosumab is estimated at 8 per 10000 per month, and 2 per 1000 over three months (9). Similarly, Stopeck et al. reported a probability of 0.06% (0.0006)[7] .

Conclusion: *Denosumab (Xgeva®) is considered a reference treatment strategy for preventing bone complications related to bone metastases in breast cancer by delaying serious skeletal events such as pathological fractures and spinal cord compression. Careful monitoring is essential to manage potential side effects, including osteonecrosis of the jaw and hypocalcaemia.*

Keywords: breast cancer, denosumab, bone metastases, skeletal-related events.

Introduction:

Breast cancer is the leading cause of cancer mortality among women globally, with over 90% of these deaths attributed to metastasis [1]. Among patients with metastatic breast cancer, approximately 65% to 75% develop bone metastases [1, 2]. These lead to severe skeletal-related events (pain, pathological fractures, spinal cord compression, hypercalcemia), which significantly impair patients' quality of life. Bone-targeting agents, particularly denosumab (Xgeva), are now the therapeutic standard. Their demonstrated efficacy in numerous randomized clinical trials is a result of a better understanding of the pathophysiology of bone metastases, which has led to more adapted prevention and management strategies. Normal bone formation is a dynamic and harmonized process involving the synthesis of bone tissue by osteoblasts and its remodeling and resorption by osteoclasts. This delicate balance is regulated by various local and systemic factors such as TGF-β (transforming growth factor-beta), IGF (insulin-like growth factor), bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), prostaglandins, parathyroid hormone, and RANK-L, a key element in osteoclast differentiation [3]. Bone metastases disrupt this balance through a complex process that includes tumor dissemination, implantation into bone tissue, cell proliferation, and angiogenesis. RANKL (Receptor Activator of Nuclear Factor kappa B Ligand) is a key regulator of osteoclastogenesis and bone resorption[4]. It exists in three molecular forms and is primarily produced by osteocytes, though it is also found in osteoblasts, activated T lymphocytes, and immune cells. When RANKL binds to its receptor, RANK, on osteoclast precursors and mature osteoclasts, it triggers their differentiation into functional, multinucleated osteoclasts. Conversely, osteoprotegerin (OPG) acts as a natural inhibitor by binding to RANKL and preventing its interaction with RANK[5]. Notably, RANKL also has a pro-migratory effect, promoting bone metastases via parathyroid hormone-related protein (PTHrP) production by breast cancer cells [6].

Mechanism of Action of RANKL Inhibitors:

Denosumab is a fully human monoclonal antibody specifically directed against RANKL. It acts by binding to the DE loop region of RANKL, whether in its soluble or membrane-bound form, on target cells[7]. Mimicking the action of osteoprotegerin (OPG), but with a significantly higher affinity for RANKL, denosumab effectively blocks the interaction between RANKL and its receptor, RANK. This mechanism inhibits the differentiation, activation, and survival of osteoclasts. By doing so, it prevents the neoplastic mononuclear stromal cells characteristic of giant cell tumors of bone (GCTB)

from activating osteoclastic giant cells[8,9] . This mechanism ultimately prevents bone resorption induced by the activity of these giant cells[7].

Indications of Denosumab :

Denosumab is a fully human monoclonal antibody that targets RANKL, thereby inhibiting osteoclast activity and reducing bone resorption. There are two commercial forms: Prolia® (60 mg), primarily used for postmenopausal osteoporosis treatment, and XGEVA® (120 mg), which is the focus of this literature review.

XGEVA® has several key indications:

- **Prevention of Skeletal-Related Events (SREs):** XGEVA is the current standard for preventing bone complications associated with bone metastases. Its addition to chemotherapy in patients with metastatic breast cancer to the bone [10] has demonstrated superiority over bisphosphonates in delaying or preventing SREs[10, 11–13].
- **Treatment of Symptomatic Bone Metastases:** Beyond its preventive role, XGEVA is indicated for treating symptomatic bone metastases, including those originating from prostate and lung cancers[9] .
- **Treatment of Giant Cell Tumors of Bone (GCTB):** Denosumab (XGEVA) received approval from the U.S. Food and Drug Administration (FDA) in 2013 and the European Medicines Agency (EMA) in 2014 for treating skeletally mature adults and adolescents with unresectable GCTB or when surgical resection is likely to result in severe morbidity[14, 15].
- **Treatment of Malignant Hypercalcemia:** Since 2012, numerous articles have reported denosumab's efficacy in patients with cancer-associated hypercalcemia in tumors such as multiple myeloma, renal cell carcinoma, ovarian cancer, and parathyroid carcinoma[16, 17] .

Materials and Methods:

We conducted a literature review to assess the impact of denosumab (Xgeva) in preventing bone metastases related to breast cancer. Our search utilized two scientific databases: PubMed and MEDLINE. The following keywords were used: "breast cancer," "denosumab," and "bone metastases." The article selection process was as follows: Articles published from 2014 to 2025 were selected. Initial selection was based on the keywords. Articles not relevant to our research theme were excluded. One hundred forty articles were initially identified. After reviewing their abstracts, thirty-one were selected for further evaluation. Of these, twenty were ultimately included after a full-text review.

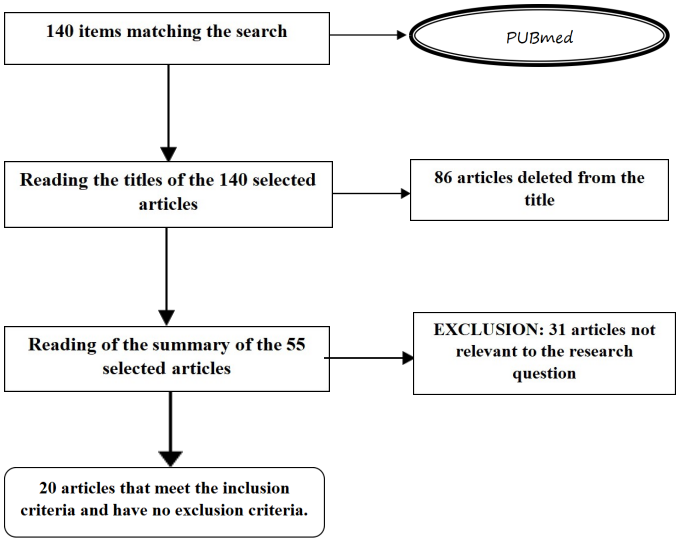

Figure 1: Flowchart illustrating the search results and the method for selecting the retained articles.

Results:

Various studies have highlighted several effects of denosumab treatment in breast cancer patients with bone metastases. These results concern both the associated complications and the observed benefits on skeletal-related events. We present below the

main data, grouped according to the types of complications and effects observed:

Impact of Denosumab (XGEVA) on the Prevention of Skeletal-Related Complications and Events:

- **Time to First Skeletal Complication:** Several clinical studies have shown that denosumab (Xgeva) significantly delays the occurrence of the first skeletal-related event in patients with breast cancer and bone metastases. As demonstrated by the study from Luca Mastrantoni, this treatment prolongs the time until the first fracture (HR: 0.760; 95% CI: 0.666–0.869)[3]. Denosumab (Xgeva) reduces the risk of skeletal complications by 14% to 24% [19, 27, 30, 32]. Studies have reported a median time to the first SRE ranging from 12 to 44.55 months[6, 7, 11, 14, 32–34].
- **Skeletal-Related Events:** Luca Mastrantoni showed a significant reduction in fractures in pre- and postmenopausal women (RR: 0.787; 95% CI: 0.696–0.890). Specifically, premenopausal patients had an RR of 0.771 (95% CI: 0.589–1.009), while postmenopausal patients had an RR of 0.794 (95% CI: 0.692–0.912). Denosumab treatment also delayed the time to first fracture (HR: 0.760; 95% CI: 0.666–0.869), with a consistent treatment effect in both premenopausal (HR: 0.740; 95% CI: 0.557–0.984, $p < 0.01$) and postmenopausal patients (HR: 0.764; 95% CI: 0.657–0.887) (19). At 72 months, the cumulative incidence of fractures was 14.2% for denosumab and 10.7% for placebo, with an absolute difference ranging from 2.39% to 3.5% [19, 20, 25]. This also represented a 23% decrease compared to treatment with zoledronic acid (ZA) [9]. Furthermore, an 18% reduction in fracture risk was observed [10, 33], along with a specific 7.7% reduction over a one-year period [34]. Benjamin G. Wajda, for his part, reported a notable and significant reduction in fracture occurrence of up to 39% [4].
- **Bone Pain:** Regarding bone pain, Taiki Yasukawa [11] indicated that at 12 months post-surgery, the patient was able to walk without pain. In another article, Lipton et al. [12] demonstrated that denosumab treatment significantly delayed the onset or worsening of pain in patients with moderate to severe pain, with a 17% reduction in risk ($p = 0.003$). According to Coleman et al. [10], a notable improvement in health-related quality of life (HRQoL) was observed in 10% of patients treated with denosumab compared to those on zoledronic acid, regardless of initial pain intensity.

According to Benjamin G. Wajda [4], denosumab is more effective than zoledronic acid in delaying pain worsening in patients with no pain or mild pain at the beginning (HR 0.70; 95% CI 0.70–0.90; $p = 0.0002$). It is also more effective in delaying increased pain interference in patients who had no pain at the beginning (HR 0.86; 95% CI 0.77–0.96; $p = 0.010$). Additionally, in patients who were not on analgesic treatment or received few analgesics at baseline, the median time to initiation of strong opioid treatment was not reached in the denosumab group, unlike the zoledronic acid group, which had a median time of 29.5 months [4]. These articles highlight the effectiveness of denosumab in reducing and controlling bone pain.

- **Spinal Cord Compression:** A 0.5% reduction in spinal cord compression was observed [14]. According to Charles L., the probability of spinal cord compression occurring with denosumab is estimated at 8 per 10,000 per month, and 2 per 1,000 over a three-month period [9]. A

study by Stopeck et al. reported a probability of 0.06% (0.0006) [CI: 0.0006, 0.0007] [7]. In a study by Wei Li, 3 cases of spinal cord compression were observed among 50 patients on denosumab [13]. Furthermore, Megan Bradley's study [8] reported a 2.6% reduction in spinal cord compressions, with a relative risk (RR) of 0.96 [95% CI: 0.54–1.70; p = 0.88].

Adverse Effects of Denosumab

- **Hypocalcemia:** Hypocalcemia is a frequent complication associated with denosumab (Xgeva) treatment. Several studies report an incidence ranging from 7% to 15.1% [3–7, 33, 35, 36]. Wei Li and Mingchuan Zhao show a significantly increased risk with severe cases (Grade III/IV) and an incidence ranging from 2% to 68% [13, 34].
- **Osteonecrosis of the Jaw**: Osteonecrosis of the jaw (ONJ) is a well-established complication of denosumab (Xgeva) treatment, with a reported incidence ranging from 1% to 11.6% [3, 9, 10, 12, 13, 33, 34, 37]. Furthermore, periodontitis was observed in 28% of patients [13], and a high incidence of ONJ was also noted in Benjamin's article (RR 1.43; 95% CI 1.03–1.97; p = 0.032) compared to zoledronic acid [4], highlighting the need for enhanced dental monitoring.

Table 1: Summary of articles selected for the literature review on the impact of denosumab (Xgeva) in preventing complications from bone metastases associated with breast cancer:

Article	Trials	Events related to the skeleton	Time to onset of first bone complication	Occurrence of osteonecrosis of the jaw	Hypocalcemia
Adjuvant denosumab dans le cancer du sein précoce : une revue systématique et une méta-analyse des essais cliniques contrôlés randomisés . (3)	Two phase III trials included: ABCSG-18 and D-CARE, totaling 7,929 patients.	Significant reduction in fracture incidence with denosumab (RR: 0.787; 95% CI: 0.696–0.890). Decreased fracture risk in pre- and post-menopausal populations.	Denosumab delays the time to first fracture (HR: 0.760; 95% CI: 0.666–0.869).	Higher incidence with denosumab (5%) compared to placebo (<1%) in the D-CARE trial.	Hypocalcemia occurred in 7% of patients treated with denosumab compared with 4% of patients receiving placebo in the D-CARE trial
A Retrospective Analysis of Denosumab for the Treatment of Bone Metastases in Chinese Patients With Breast Cancer. (13)	Retrospective study conducted from September 2020 to January 2022. 50 patients with bone metastases from breast cancer treated with denosumab (120 mg SC every 4 weeks) in a hospital in China.	Incidence of SREs after 1 year: - 5 pathological fractures in 50 patients. - Total SRE rate after 1 year: 24% (12 patients out of 50). - 3 cases of spinal cord compression in 50 patients.	24% of patients developed bone events within one year of treatment.	Periodontitis 28.0%. Osteonecrosis of the jaw 4.0%.	68% of patients developed hypocalcemia while taking Denosumab. 2% of cases were grade III/IV (severe hypocalcemia)
Successful treatment of atypical femoral fracture with autogenous bone grafting in a patient on denosumab for bone metastasis from breast cancer: A case report .(11)	Observational study	Occurrence of a complete subtrochanteric fracture of the right femur. Twelve months after surgery and treatment with denosumab, the patient was able to walk without pain.	2 years after discontinuing denosumab.	Not mentioned in this study.	Not mentioned in this study.
Real-life use of denosumab 120 mg every 12 weeks in prolonged treatment over 2 years of patients with breast cancer bone metastases. (35)	Observational study 22 patients with breast cancer bone metastases.	-Vertebral fractures. -Rebound fractures. -Spinal cord compression.	Not mentioned in this study.	The incidence of ONJ was no higher with denosumab than with zoledronic acid (p = 0.39) [36].	Two patients corresponding to 9% of the study population.

Cost-effectiveness of denosumab for the prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. (14)	An integrated analysis of data from three phase 3 trials designed as randomized, double-blind trials involving 5,723 patients.	Reduction in the risk of spinal cord compression by 0.5%.	1.4 years	Not mentioned in this study.	significantly higher difference in the denosumab arm compared to zoledronic acid. p=0.0060.
Denosumab treatment is associated with the absence of circulating tumor cells in patients with breast cancer. (38)	Study of 73 patients with invasive breast cancer with bone metastases, treatment with denosumab versus no treatment.	Not mentioned in this study.	No statistical difference in the incidence of hypocalcemia in patients with tumor burden and circulating tumor cells compared to patients without CTC (p=0.698)	Not mentioned in this study.	List only as a known side effect of Denosumab.
Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics. (12)	3 randomized, double-blind phase III trials	Reduced risk (event occurrence in 341/1141 in the denosumab arm vs. 396/1120 in the zolidronic acid arm). -Denosumab reduces the risk of moderate/severe bone pain by 17%; p=0.003.	Significantly prolonged time to onset in the Denosumab arm (median not specified in main table).	Slight increase in risk (≈2%).	Not mentioned in this study
Denosumab versus pamidronate in the treatment of osteolytic bone metastases secondary to breast cancer: a multi-institutional analysis. (8)	Multicenter analysis using the TriNetX database. 847 patients with bone metastases from breast cancer treated with denosumab or pamidronate.	-Reduction in fractures with Denosumab: 2.7%, compared to 2.8% for pamidronate (no statistically significant difference, p = 0.88) -Decrease in spinal compression of 2.6% with denosumab versus 2.7% with pamidronate (RR 0.96, confidence interval 0.54, 1.70, p = 0.88).	Not mentioned in this study	Not mentioned in this study	Not mentioned in this study
Effect of denosumab versus zoledronic acid on calcium levels in cancer patients with bone metastasis: A retrospective cohort study. (6)	Retrospective cohort study conducted from August 2015 to July 2016, involving 271 patients with bone metastases from cancer (mainly breast cancer). Comparison between denosumab (120 mg SC every 4 weeks) and zoledronic acid (4 mg IV every 4 weeks).	Reduction in fracture risk in the Denosumab group: 2.7% vs. 2.8% in the Zoledronic Acid group.	24% of patients treated with Denosumab developed one or more serious skeletal events (SREs) after 1 year of treatment. 25% of patients treated with Zolidronic acid developed one or more serious skeletal events (SREs) after 1 year of treatment.	More common in the zolidronic acid arm	5.5% for denosumab vs. 3.1% for zoledronic acid (p = 0.05).
Cost-Effectiveness Analysis of Denosumab in the Prevention of Skeletal-Related Events Among Patients With Breast Cancer With Bone Metastasis in India. (7)	Cost-effectiveness analysis based on a Markov model simulating outcomes in 1,000 patients with bone metastases from breast cancer. Comparison of denosumab (120 mg SC every 4 weeks) with zoledronic acid (ZA) administered every 4 weeks and every 12 weeks.	-Reduction in pathological fractures under denosumab: 2.39 (for Luminal A) versus 2.78 under ZA. - The probability of the first spinal cord compression occurring in patients treated with denosumab is 0.06% CI [0.0006, 0.0007].	The exact timing of the first SRE (severe skeletal event) is not specified precisely.	Not mentioned in this study	Not mentioned in this study
Bone Health Outcomes from the International, Multicenter, Randomized, Phase 3, Placebo-Controlled D-CARE Study Assessing Adjuvant Denosumab in Early Breast Cancer. (39)	International, multicenter, randomized, double-blind phase III clinical trial: D-CARE.	The risk of fractures was reduced with denosumab (HR 0.76, 95% CI: 0.63-0.92) compared to placebo. The risk of fracture is reduced by 24% with denosumab compared to placebo.	Rate of first SREs after bone metastasis: 1.7% with denosumab vs. 3.2% with placebo. HR: 0.52 (95% CI: 0.35–0.78), p = 0.001.	Not mentioned in this study.	Not mentioned in this study.

Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance). (9)	Cost-effectiveness analysis based on the CALGB/ Alliance 70604 study, comparing monthly denosumab with monthly or quarterly zoledronic acid (ZA) in women with bone metastases from breast cancer.	Denosumab reduces the risk of pathological fractures and other serious skeletal events (SREs) more effectively than ZA: 23% reduction in the risk of SREs compared to monthly ZA. Probability of spinal cord compression: • Denosumab: 0.0008/month • Monthly zoledronic acid: 0.0020/month • Zoledronic acid every 3 months: 0.0008/month -Probability of subsequent spinal cord compression: • Denosumab: 0.0020/ month • Monthly zoledronic acid: 0.0004/month • Zoledronic acid every 3 months: 0.0010/month.	Probability of first pathological fracture: • Denosumab: 0.0193/month (1.93%) • Monthly zoledronic acid: 0.0027/month (0.27%) • Zoledronic acid every 3 months: 0.0032/ month (0.32%) -Probability of subsequent fractures: • Denosumab: 0.0473/month (4.73%) • Monthly zoledronic acid: 0.0014/month (0.14%) • Zoledronic acid every 3 months: 0.0017/ month (0.17%)	The incidence is 1% for Denosumab vs. 2% for Zoledronic Acid..	Frequent complication.
First prospective data on breast cancer patients from the multicentre Italian bone metastasis database.(32)	Italian multicenter prospective study (2021) on 220 patients with bone metastases from breast cancer.	Not mentioned in this study.	For patients treated with zoledronic acid or pamidronate, the HR for the occurrence of first skeletal-related events (SREs) is 1.32 (95% CI: 0.74–2.38). The HR for patients treated with denosumab is 0.20 (95% CI: 0.04–0.87), an 80% reduction in the risk of first skeletal-related events (SREs).	Not mentioned in this study	Not mentioned in this study
Severe Refractory Hypocalcemia Caused by Denosumab. (36)	Case report of a 68-year-old female patient with metastatic bone cancer treated with Denosumab.	No pathological fractures were reported in this patient receiving Denosumab.	Not mentioned in this study	Not mentioned in this study	Only one patient who developed severe, refractory hypocalcemia.
Bone health in cancer patients: ESMO Clinical Practice Guidelines. (10)	Phase III, randomized, prospective clinical trial.	-18% reduction in SRE risk with Denosumab compared to zoledronic acid Hazard Ratio (HR) = 0.82 (95% CI: 0.71–0.95; p=0.01).	Not mentioned in this study.	1.8% with denosumab vs. 1.3% with zoledronic acid.	Not mentioned in this study
A Comparison of the Efficacy and Safety of Denosumab and Zoledronic Acid in Patients with Bone Metastatic Breast Cancer Receiving CDK4/6 Inhibitor Therapy. (33)	Retrospective, single-center study of 328 patients with metastatic bone cancer receiving a CDK4/6 inhibitor + endocrine therapy.	Fractures are likely included in SREs, showing that denosumab reduces the overall risk of serious skeletal events (SREs) compared to zoledronic acid. Hazard Ratio (HR) = 0.82, thus reducing the overall risk of SREs by 18% compared to zoledronic acid.	Median time to first SRE: 44.55 months for denosumab versus 29.16 months for zoledronic acid.	6.7% in patients receiving denosumab versus 4.0% with zoledronic acid (p=0.289).	Incidence with denosumab: 15.1% vs. 7.4% with zoledronic acid (p=0.030)

A multicenter, randomized, double-blind trial comparing LY01011, a biosimilar, with denosumab (Xgeva®) in patients with bone metastasis from solid tumors. (34)	Phase III multicenter, randomized, double-blind clinical trial.	-Reduction in fractures: 7.7% of patients treated with denosumab experienced an SRE during the one-year study period. -9.0% of patients treated with LY01011 (the biosimilar) experienced an SRE during the same period.	The median time to first SRE is 26.4 months with denosumab, which is longer than with LY01011 (24.8 months).	One case (0.1%) of dental pain was observed in the denosumab group, while no cases were reported in the LY01011 group.	-LY01011 : 28,1 % - Denosumab : 25,9 %
Adjuvant denosumab for early breast cancer–Evidence and controversy. (5)	Randomized study (D-CARE) involving 4,509 patients at high risk of recurrence.	Réduction significative des fractures osseuses (HR 0,76, p = 0,0037).	This study did not show any significant difference in the time to onset of bone metastases (BMFS) between Denosumab and placebo.	Not mentioned in this study	-11 % des patientes ont présenté de l'hypocalcémie.
Denosumab vs. Zoledronic Acid for Metastatic Bone Disease: A Comprehensive Systematic Review and Meta-Analysis of Randomized Controlled Trials. (4)	7 randomized controlled trials involving 7,441 patients.	Significant reduction in pathological fractures in breast cancer (39%) (RR 0.61; 95% CI 0.39-0.94).	Longer time to first skeletal event, greater than ZA (RR 0.86; 95% CI 0.80-0.93; p < 0.01) compared with zoledronic acid.	Higher incidence of osteonecrosis of the jaw (RR 1.43; 95% CI 1.03 –1.97; p = 0.032) compared with zoledronic acid.	-Significant increase in the risk of hypocalcemia p < 0.0001 vs zoledronic acid

Discussion:

Bone complications associated with breast cancer metastases, particularly pathological fractures and spinal cord compression, are major detrimental events that cause significant morbidity and a considerable decline in quality of life.

Denosumab (Xgeva) has emerged as an important therapy in managing these bone complications of breast cancer. The body of evidence presented in our literature review—including randomized clinical trials, retrospective analyses, and meta-analyses—converges on the demonstrated efficacy of denosumab in preventing skeletal-related events (SREs).

Our literature review highlighted that denosumab delays the occurrence of the first SRE. Irem Öner reported an extension of the median time to SRE onset, reaching 44 months compared to approximately 29 months in patients treated with zoledronic acid [33].

Benjamin G. Wajda [4] and Laura Moretti [5] demonstrated a significant reduction in pathological fractures in breast cancer patients with bone metastases, with a risk reduction of 39% and 24%, respectively [27, 32].

Despite the severe nature of SREs, which are a source of bone pain, our literature review indicates that denosumab is also effective in treating this pain. The study by Yasukawa et al. [11] reported satisfactory functional recovery one year after surgery. The results from Lipton et al. [12] indicate a notable 17% decrease in the risk of pain amplification. It is also worth mentioning that, according to Benjamin G. Wajda's article [4], denosumab treat-

ment leads to a notable delay in opioid use, suggesting more effective pain management.

In comparison to zoledronic acid, there does not appear to be a difference in the prevention of spinal cord compression. Charles L. [9] estimates the monthly probability of spinal cord compression with denosumab (Xgeva) to be between 8/10,000 per month and 2/1,000 over three months. Stopeck et al. reported a probability of 0.06% (0.0006) [CI: 0.0006, 0.0007] [7], with a 2.6% reduction in spinal cord compression [a relative risk (RR) of 0.96 (95% CI: 0.54–1.70; p = 0.88)] [8]. This could reflect a modest but clinically relevant benefit in terms of reducing this type of complication.

These findings position denosumab (Xgeva) as a benchmark therapeutic strategy for preventing bone complications associated with breast cancer metastases [10].

Nevertheless, the clinical benefits of denosumab (Xgeva) must be balanced against its non-negligible safety profile. Several studies have reported an increased risk of osteonecrosis of the jaw (ONJ), with an incidence of up to 11.6% [3, 9, 10, 12, 13, 33, 34, 37], which is significantly higher than that observed with bisphosphonates.

Furthermore, hypocalcemia is a frequently observed adverse effect, with rates ranging from 7% to 11% [3–6, 14, 35], sometimes including severe Grade III or IV forms [13]. These data emphasize the need for rigorous biological monitoring, appropriate calcium and vitamin D supplementation, and a thorough dental evaluation before initiating treatment.

Limitations of the Available Data

It is important to highlight some methodological limitations in our literature review. Among the studies examined, a significant number of them rely on retrospective data or have selection biases that could influence the results.

Furthermore, the heterogeneity of the protocols—in terms of administration frequency, follow-up duration, and patient inclusion criteria—makes it difficult to perform a rigorous and standardized comparison of the available data.

Finally, it is important to note that few studies evaluate the effectiveness of denosumab (Xgeva) beyond two years, and the potential long-term consequences of its discontinuation remain largely unknown.

Conclusion

Denosumab (Xgeva) is a monoclonal antibody that targets RANKL and is used to prevent bone complications associated with breast cancer metastases. Its use helps delay the onset of the first skeletal-related event. Its effectiveness has been demonstrated in reducing the incidence of pathological fractures and spinal cord compression. However, adverse effects such as hypocalcemia and osteonecrosis of the jaw can occur, which necessitate rigorous clinical monitoring. Despite some limitations in this literature review, the reported data support the use of denosumab (Xgeva) in patients with breast cancer and bone metastases. It is beneficial both for preventive use before symptoms appear and for treating existing complications. Before starting treatment, precautions should be taken, including a dental examination with appropriate preventive care, a calcium assessment, and close monitoring for side effects.

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