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The use of osteoclast inhibitors in metastatic breast cancer

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Abstract

Introduction: In most patients, metastatic breast cancer (MBC) is incurable. Consequently, the goal in this setting is life prolongation and quality of life improvement, although possible long-term effects of anticancer treatment need to be considered. Bone is the most common site of metastasis in breast cancer and its complex management includes minimizing the risk of skeletal-related events (SRE), maximizing pain control, stabilizing or even restoring function, preventing spinal cord compression, hypercalcemia of malignancy and fractures and reducing the need for radiotherapy and orthopedic surgery.

Aim: The present paper aims to compare the efficacy and safety of zoledronic acid (and other bisphosphonates) with denosumab in the management of bone metastases in breast cancer patients.

Materials and methods: In this article, required information was collected through literature review and keyword query using the PRISMA 2020 guideline.

Conclusions: In the metastatic setting, it appears that denosumab is indeed superior to zoledronic acid in delaying and preventing skeletal related events, except for spinal cord compression and risk of surgery, and equally efficient in treatment of already present bone pain and hypercalcemia of malignancy, with similar adverse effects, overall survival and disease progression.

Keywords: metastatic breast cancer, osteoclast inhibitors, bisphosphonates, zoledronic acid, denosumab

Abbreviations: CI = confidence interval, CT = computer tomography, I.V. = intravenous, MBC = metastatic breast cancer, MRI = magnetic resonance imaging, OR = odds ratio, p = probability, PET = positron emission tomography, S.C. = subcutaneous, SRE = skeletal related events

Introduction

Bone metastases are a frequent manifestation of distant recurrence in many types of solid cancer, especially those arising in the breast. They cause important morbidity, with debilitating symptoms and potential life-threatening complications.

Aim

The present paper aims to compare the efficacy and safety of zoledronic acid (and other bisphosphonates) with denosumab in the management of bone metastases in breast cancer patients.

Materials and methods

In this article, required information was collected through literature review and keyword query using the PRISMA 2020 guideline.

Screening and diagnosis

Detection procedures include X-ray, bone scintigraphy, computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography (PET) scan, although the clinical presentation and primary cancer histologic type should guide the choice of imaging. Considering that in breast cancer bone metastases develop predominantly mixed – osteoblastic and osteolytic – patterns, bone scintigraphy is generally indicated. All these taken into consideration, spinal disease should be evaluated by MRI [1].

Osteoclast inhibitors and skeletal related events

Skeletal related events are defined as: bone pain, pathologic fracture, spinal cord compression, hypercalcemia of malignancy and bone radiation or surgery. These are relatively frequent consequences of secondary

breast cancer to the bone, Oster et al. (2013) having identified the cumulative incidence of skeletal related events to be 38%, 45% and 54% at 6, 12 and 24 months of follow-up, respectively, and lead to an important decrease in quality of life and increase in morbidity and mortality [2-4].

The incidence of the first skeletal related event is highest in the first year following the diagnosis of metastatic breast cancer to the bone, and in 22% of cases skeletal related events are present at the moment of diagnosis [3,5].

Denosumab proved superior to zoledronic acid in both delaying and preventing the skeletal related events and in improving the patients' quality of life. There were no major differences in adverse effects, overall survival and disease progression between the two [6,7].

Osteoclast inhibitors effect on pain

Pain is present in up to 67% of secondary breast cancer to the bone and significantly decreases quality of life. Fewer patients treated with denosumab, compared to zoledronic acid, suffered a clinically relevant worsening of pain. Also, denosumab treatment led to a longer delay in pain worsening and a lower need for opioid use. Clinically relevant pain relief occurred after similar periods of time in both treatment options [6,8,9].

Thus, denosumab proved to be superior to zoledronic acid in preventing bone pain and reducing opioid use, but equivalent to it in treatment of already present pain [9].

Osteoclast inhibitors effect in disease related fractures

Pathologic fractures decrease mobility, increase mortality and occur in up to 35% of metastatic breast cancer to the bone [8,10].

Both zoledronic acid and denosumab increase bone mass density, albeit through different mechanisms and in different regions. Those treated with denosumab for bone

metastases have a lower pathologic fracture risk (21%) compared to those treated with zoledronic acid (23%), possibly due to denosumab's cortical bone porosity decreasing effect [11-13].

Denosumab treatment discontinuation carries an increased risk of "rebound" vertebral fractures. This rebound effect was found to last 2 years. Why these occur is unclear, but it is considered likely that they are caused by increased osteoclast-mediated bone resorption because of sudden reactivation of dormant osteoclast precursors and high expression of RANKL [14,15].

Spinal cord compression

Spinal cord compression is identified in up to 11% of patients with metastatic breast cancer to the bone and usually presents as an oncological emergency. Most frequently, it is caused by the compression fracture of a vertebra, but it can also happen because of direct tumoral invasion [16,17].

Bisphosphonates do not alter spinal cord compression odds ratio (OR 0.71, confidence interval CI 95%, 0.47-1.08, p value = 0.113) and denosumab use was shown to decrease it, but not significantly (OR 0.92, CI 95%, 0.66-1.28, p = 0.66). Overall, denosumab was not found to be significantly superior to zoledronic acid in decreasing spinal cord compression risk in metastatic breast cancer to the bone [18,19].

Hypercalcemia of malignancy

Hypercalcemia of malignancy is an oncological emergency associated with a poor

prognosis and can result in coma or even death. Breast cancer is one of its most common oncological causes [20].

Denosumab is more effective in both delaying and preventing the first and subsequent episodes of hypercalcemia, compared to zoledronic acid, but they are equally efficient in correcting it when already present. Denosumab might be an alternative to zoledronic acid as first-line treatment of hypercalcemia of malignancy [21,22].

Denosumab therapy discontinuation can lead to rebound hypercalcemia, especially in patients with an immature skeleton [23].

Bone radiation therapy and surgery

While increasing quality of life when they are necessary, bone radiation therapy and orthopedic surgery can also increase patient morbidity. For example, bone surgery can result in local events, infection, thrombosis and hemorrhage, among others, while irradiation degrades bone structure and damages bone marrow [24-26].

Denosumab proved to be the most effective in reducing the need for radiation (OR 0.51, CI 95%, 0.35-0.75), followed by pamidronate (OR 0.67, CI 95%, 0.52-0.86) and zoledronic acid (OR 0.70, CI 95%, 0.52-0.96). The only osteoclast inhibitor that reduced the risk of surgery was pamidronate (OR 0.60, CI 95%, 0.37-0.98) [27].

Toxicity associated with osteoclast inhibitors (Table 1,2)

Table 1. Bisphosphonates [28-30]

Administration route	Adverse effects	Comments
Oral and I.V.	Hypocalcemia <ul style="list-style-type: none"> • Paresthesias (peri-oral, extremities) • Muscle twitching, spasms • Seizures 	Common More frequently after I.V. administration Patients using bisphosphonates should take calcium and vitamin D supplements

	Musculoskeletal pain	Common It may be severe and symptoms do not always resolve completely after discontinuation
	Renal toxicity <ul style="list-style-type: none"> Renal impairment Acute renal failure 	Common Bisphosphonates are not recommended for use in patients with CrCl < 30 mL/ min Adequate hydration is required prior to each infusion
	Hematological <ul style="list-style-type: none"> Anaemia Thrombocytopenia Leucopenia 	Uncommon
	Ocular side effects <ul style="list-style-type: none"> Pain Blurred vision Conjunctivitis Uveitis Scleritis 	Rare
	Atrial fibrillation	Common
	Osteonecrosis of the jaw <ul style="list-style-type: none"> Pain Swelling Exposed bone Local infection Pathologic fracture of the jaw 	Rare Risk is higher with I.V. administration Requires discontinuation Good oral hygiene and regular dental visits are especially encouraged in bisphosphonate-receiving patients
	Atypical femur fractures	Rare complication of chronic therapy (median treatment time - seven years)
	Neuropsychiatric <ul style="list-style-type: none"> Insomnia Headache Dizziness 	Uncommon
Oral	Gastrointestinal <ul style="list-style-type: none"> Reflux Esophagitis Ulcers Esophageal cancer 	Incidence is very low if proper administration instructions are followed
I.V.	Flu-like symptoms Acute-phase reaction: <ul style="list-style-type: none"> Low-grade fever Myalgia Headache Arthralgia 	Common Antipyretic drugs generally improve symptoms (ibuprofen, acetaminophen) The recurrence of symptoms decreases with subsequent infusions

Table 2. Denosumab [31-33]

Administration route	Adverse effects	Comments
S.C. in the upper arm, thigh or the abdomen every 6 months	Osteonecrosis of the jaw	Rare Pretreatment considerations are the same as those for bisphosphonates
	Increased vertebral fractures risk with discontinuation or missed doses	Patients should not have a drug pause Alternative therapy is advised (bisphosphonates)
	Musculoskeletal pain	Common
	Infections requiring hospitalization: <ul style="list-style-type: none"> • Cellulitis • Diverticulitis • Pneumonia • Appendicitis • Labyrinthitis 	Uncommon In any of these cases, the patient should present to the hospital
	Hypocalcemia	Common
	Osteonecrosis of the external auditory canal	Rare
	Cystitis	Common
	Sciatica	Common
	Atypical femur fractures	Rare
	Rash	Common

Conclusions

In the metastatic setting, it appears that denosumab is indeed superior to zoledronic acid in delaying and preventing skeletal related events, except for spinal cord compression and risk of surgery, and equally efficient in treatment of already present bone pain and hypercalcemia of malignancy, with similar adverse effects, overall survival and disease progression.

Conflicts of interest

The authors state no conflict of interest.

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