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Review Article

Bone targeted therapy for preventing skeletal-related events in metastatic breast cancer

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ABSTRACT

Cancer cells can alter physiological mechanisms within bone resulting in high bone turnover, and consequently in skeletal-related events (SREs), causing severe morbidity in affected patients. The goals of bone targeted therapy, as bisphosphonates and denosumab, are the reduction of incidence and the delay in occurrence of the SREs, to improve quality of life and pain control.

The toxicity profile is similar between bisphosphonates and denosumab, even if pyrexia, bone pain, arthralgia, renal failure and hypercalcemia are more common with bisphosphonates, while hypocalcemia and toothache are more frequently reported with denosumab. Osteonecrosis of the jaw (ONJ) occurred infrequently without statistically significant difference.

The present review aims to provide an assessment on bone targeted therapies for preventing the occurrence of SREs in bone metastatic breast cancer patients, critically analyzing the evidence available so far on their effectiveness, in light of the different mechanisms of action. Thus, we try to provide tools for the most fitting treatment of bone metastatic breast cancer patients.

We also provide an overview on the usefulness of bone turnover markers in clinical practice and new molecules currently under study for the treatment of bone metastatic disease.

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Contents

1. Introduction

Bone health is an important tool in the management of breast cancer (BC) patients. BC is the most common osteotropic tumor and bone

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represents the first site of relapse for approximately 50% of affected patients [1].

Approximately 70% of patients with advanced BC experience bone metastases [2], which can lead to the so-called skeletal-related events (SREs), associated with substantial morbidity in terms of severe pain, loss of autonomy and negative impact on quality of life. Most clinical trials define an SRE as pathologic fracture (vertebral and/or non-vertebral), radiation therapy to bone, surgery to bone and spinal cord compression. The definition may or may not include hypercalcemia of malignancy (HCM) [3]. The frequency of skeletal events depends on the nature of bone lesions (blastic or osteolytic), their location and number, as well as the management and treatment of complications. Pain is the most common symptom [4].

Several clinical studies showed that high bone turnover is associated with a significantly higher risk of SREs, disease progression and death in metastatic breast cancer (mBC) patients. Normally, in the "basic multicellular unit" (BMU), the area of bone remodeling [5], many stimuli (PTH, PTH-rP, IL-8, IL-6 and IL-1) may activate osteoblasts to express RANKL and the soluble form sRANKL acting on a receptor present on the surface of the monocyte precursor of osteoclasts (RANK), thus turning them into activated osteoclasts. Osteoblasts produce osteoprotegerin (OPG) that binds to RANKL and inhibits the activation of osteoclast precursors and thus bone resorption. The main regulator of osteoblast activity is the Wnt/β-catenin signaling pathway. Wnt regulates OPG expression by osteoblasts, inhibiting osteoclast activity. By binding to the frizzled/LRP-receptor (LRP5/6), Wnt prevents the degradation of β-catenin, which in turn translocates into the nucleus and facilitates OPG transcription.

Cancer cells can alter physiological mechanisms within bone. They can secrete the antagonist of Wnt, Dkk-1, which, by binding the Wnt co-receptor LRP5/6, inhibits the production of OPG, contributing to increase osteoclast activity in the metastatic bone lesion [6]. Development of osteolytic or osteosclerotic lesions depends on the number and function of osteoblasts. Osteolytic lesions are characterized by inhibition of osteoblast differentiation and activity, at least partially related to high levels of activin and Dkk-1. In contrast, tumor cell-derived endothelin-1, through the inhibition of Dkk-1, induces osteoblast hyperactivity which results in disorganized new bone formation and development of osteoblastic lesions [7].

Furthermore, cancer cells can activate osteoclasts a) indirectly, by stimulating osteoblast RANKL expression via IL-8, PTH-rP, IL-6 and IL-11 and b) directly, by exhibiting an osteoblast-like pseudo-phenotype via RANK, IL-8 and MIP-1α (breast cancer cells may directly activate osteoclasts in the early stages of bone metastases via IL-8 production and via MIP-1α, naturally secreted by osteoblasts and primarily associated with cell adhesion and migration). Catepsin G overexpressed by cancer cells cuts the extracellular domain of RANK and generates active sRANKL which is critical for the activation of osteoclasts precursors. At the same time, RANKL produced by osteoblasts, beyond osteoclast activation, is attractive for cancer cells expressing RANK [6]. The bone turnover rate depends on the number of BMU at work and on duration and depth of the sequential phases of the remodeling process. Having a high bone turnover means having an increasingly higher number of penetration areas and osteoclastic bone resorption. Zheng et al. investigated the effects of high bone turnover in a model of breast cancer growth in bone, showing that increased bone turnover promotes tumor growth in bone, independent from the action of PTH.

Breast cancer patients frequently have high bone turnover due to low dietary calcium intake, vitamin D deficiency, chemotherapy, gonadotropin releasing hormone analogs, hormonal therapy, which increases the risk of SREs [8].

2. Biomarkers of bone turnover

An early identification of the risk of skeletal complications could help clinicians in optimizing the clinical management of these patients. During the metastatic process, components deriving from the skeletal metabolism, generally identified as bone formation and resorption markers, are released into the blood stream. Their detection in the serum and/or urine could allow them to be used in diagnostics and follow-up examinations, as parameters related to the skeletal prognosis and in the monitoring of therapies effect [9,10].

The cross-linked collagen peptides, breakdown products from osteolysis (e.g., the amino [N]- and carboxy [C]-terminal cross-linked telopeptides of type I collagen, or NTx and CTx), the terminal peptides cleaved from pro-collagen before its integration into new bone matrix (e.g., procollagen type I N-terminal and C-terminal peptides, or PINP and PICP) and the bone-specific alkaline phosphatase (bone ALP) are among the most intensively investigated markers of bone turnover. Among all bone remodeling markers, NTx seems to have the best diagnostic accuracy: NTx levels are proportionally related to the extension of bone involvement and to risk of SREs and have the best-established correlations with clinical outcomes and response to bone-directed therapies. In a prospective study enrolling 71 consecutive BC patients with newly diagnosed bone metastases, treated with zoledronic acid at 4 mg, every 3 or 4 weeks, baseline serum NTx levels were significantly higher in patients with blastic than lytic bone lesions and in those with multiple rather than few bone site involvement. Zoledronic acid resulted in a significant NTx reduction at first and second post-treatment evaluations performed every 2 months. More, patients with an initial NTx increase had a significantly higher rate of bone disease progression compared to those with an initial NTx reduction (66.7% versus 18.8%, $p = 0.001$) [11–14]. Also denosumab showed to suppress bone turnover and seems to reduce SRE risk similarly to bisphosphonates. When administered in intravenous (i.v.) bisphosphonates-naïve patients, it reduces serum NTx levels, at week 13 and 25 from the beginning of bone-targeted therapy, by 73–75% compared to 71–79% of bisphosphonates. On-study SREs occurred in 12% of denosumab-treated patients and 16% of i.v. bisphosphonates-treated patients [15]. However, there is little evidence supporting a role for NTx in predicting or detecting bone metastases. To date, in spite of the growing interest in evaluating the potential diagnostic, prognostic and monitoring roles of bone turnover markers in malignant bone disease, the routine use of bone markers in the clinic cannot yet be recommended [16].

3. Bone targeted therapy

The goals of bone targeted therapy (bisphosphonates and denosumab) are the reduction of incidence and the delay in occurrence of SREs. Direct consequence of the reduction of SREs is represented by an improvement in quality of life, pain control and, in some cases, increased survival [4]. About 25% of patients with bone metastases remains asymptomatic; in the remaining 75%, symptoms are related to SREs [17,18].

Few data are available on the optimal use of bone targeted therapies, mainly regarding initiation and treatment duration. To maximize their benefit, they should be initiated as soon as bone metastases are diagnosed by radiographic techniques, even if they are asymptomatic [19]. The effects of bisphosphonates on skeletal complications appear to be time-dependent. They are effective after at least 6–12 months [4]. Data from a systematic review on 30 randomized controlled trials of patients with malignant disease and bone metastases who were treated with oral or i.v. bisphosphonates showed that reduction in the need for radiotherapy was significant at six months, episodes of hypercalcemia at six months, and non-vertebral fractures at 12 months; studies of less than six months' duration did not show significant results for any skeletal morbidity outcome [20].

Since the risk of SREs is going to continue, bone targeted therapy should be prolonged beyond 2 years in order to prevent further skeletal events, while discontinuation should be limited to patients with tolerability or compliance issues. Specifically, it should not be discontinued once skeletal events occur, as controlled studies with zoledronate

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