

# Bone metastases: Causes, consequences and therapeutic opportunities

Jose Perez-Garcia, Eva Muñoz-Couselo, Javier Cortes \*

Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Medica Scientia Innovation Research (MedSIR), Barcelona, Spain

---

## 1. Introduction

Although the skeleton is a common site of metastasis for many solid tumours, metastatic bone disease is particularly relevant in prostate and breast cancers. Thus, bone is the most frequent – and often the only – location of metastasis in patients with advanced prostate cancer. Moreover, up to 70% of patients with metastatic breast cancer develop bone metastases over the course of their disease.

Metastatic bone involvement usually results in multiple skeletal complications leading to a significant deterioration in the quality of life for cancer patients. Pain, hypercalcemia and skeletal-related events (SREs) – such as the use of radiotherapy or surgery of bone, pathological fractures and spinal cord compression – are problems typically derived from bone metastases [1].

The pathogenesis of bone metastases is a complex process involving many interactions between tumour cells and osteoclasts and osteoblasts. Receptor activator of nuclear factor- $\kappa$ B (RANK) ligand (RANKL), which is expressed by osteoblasts and marrow stromal cells, is a potent inducer of osteoclast formation. In bone metastases, cytokines and growth factors secreted by tumour cells (interleukins 1 and 6, parathyroid-hormone-related peptide, tumour necrosis factor, prostaglandin E<sub>2</sub>, and macrophage-colony-stimulating factor, amongst others) increase the expression of RANKL on marrow stromal cells and osteoblasts [2]. Following this, RANKL binds to its receptor, RANK, on the surface of osteoclast precursors and stimulates the differentiation of these cells to mature osteoclasts. This excessive RANKL-induced osteoclast activity results in increased bone resorption and local bone destruction, leading to the release of growth factors from the bone matrix that subsequently promotes tumour progression. This relationship between tumour and bone cells constitutes the vicious cycle of bone metastases.

For all these reasons, patients with metastatic bone involvement who show higher levels of bone turnover mark-

ers have a particularly high risk for SREs in addition to worse clinical outcomes [3].

Treatment of bone metastases requires a broad strategy with different therapeutic options, including both local and systemic therapies. External-beam radiotherapy remains the mainstay of treatment for symptomatic bone metastases. However, considering that osteoclast-mediated bone resorption plays a critical role in the development of metastatic bone disease, its inhibition represents an attractive target for treating bone metastases. Below, some of the major management approaches are very briefly summarised.

---

## 2. Bisphosphonates

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate. These compounds are potent inhibitors of osteoclast-mediated bone resorption through two well-recognised mechanisms of action. On the one hand, first-generation non-nitrogen-containing bisphosphonates (i.e. clodronate) are metabolised by osteoclasts to cytotoxic ATP analogues; on the other hand, second- and third-generation nitrogen-containing bisphosphonates, such as zoledronic acid and pamidronate, act by inhibiting farnesyl diphosphate synthase, a key enzyme of the mevalonate pathway.

Over the last two decades these agents – in particular zoledronic acid and pamidronate – have been the most effective treatments in delaying or preventing SREs in patients with bone metastases from solid tumours, as well as in patients with multiple myeloma [4].

---

## 3. Denosumab

Denosumab is a fully human monoclonal antibody that binds to RANKL in order to inhibit osteoclast activity. Denosumab has been evaluated in three identically designed, randomised, double-blind, phase III clinical trials [5–7]. Patients were

---

\* Corresponding author. Tel.: +34 932746085.

E-mail address: [jacortes@vhio.net](mailto:jacortes@vhio.net) (J. Cortes).

1359-6349/\$ - see front matter Copyright © 2013 ECCO - the European CanCer Organisation. All rights reserved.

<http://dx.doi.org/10.1016/j.ejcsup.2013.07.035>

**Table 1 – Phase III studies with denosumab in patients with bone metastases or myeloma multiple.**

Number of patients	Type of tumour	Time to first on-study SRE	Overall survival	Time to disease progression	Refs.
1904	Prostate cancer	HR = 0.82 ( $P = 0.0002$ for non-inferiority analysis; $P = 0.008$ for superiority analysis)	HR = 1.03 ( $P = 0.65$ )	HR = 1.06 ( $P = 0.3$ )	[5]
1776	Myeloma multiple; solid tumours (except breast and prostate)	HR = 0.84 ( $P = 0.0007$ for non-inferiority analysis)	HR = 0.95 ( $P = 0.43$ )	HR = 1 ( $P = 1$ )	[6]
2046	Breast cancer	HR = 0.82 ( $P < 0.001$ for non-inferiority analysis; $P = 0.01$ for superiority analysis)	HR = 0.95 ( $P = 0.49$ )	HR = 1 ( $P = 0.93$ )	[7]

SRE, skeletal-related event; HR, hazard ratio.

randomly assigned to receive either subcutaneous denosumab 120 mg and intravenous placebo or intravenous zoledronic acid 4 mg and subcutaneous placebo every 4 weeks. The primary endpoint was time to first on-study SRE (defined as pathological fractures, the use of radiotherapy or surgery of bone, or spinal cord compression). These studies are summarised in Table 1.

Overall, adverse events and serious adverse events were similar with both treatments, although more acute-phase reactions and renal adverse events occurred in the zoledronic acid group, whereas hypocalcemia was more frequent with denosumab. Additionally, the rate of osteonecrosis of the jaw was low in both arms (~2%).

## 4. Other agents

### 4.1. Mammalian target of rapamycin (mTOR) inhibitors

mTOR inhibition decreases osteoclast maturation and increases osteoclast apoptosis, resulting in reduced bone resorption in animal models [8].

In the randomised phase III trial with everolimus in metastatic breast cancer (BOLERO-2), a total of 724 postmenopausal women with oestrogen-receptor-positive breast cancer refractory to non-steroidal aromatase inhibitor therapy were treated with exemestane and randomised (2:1) to everolimus or placebo. The addition of everolimus significantly improved median progression-free survival, the primary endpoint of this study (6.9 months versus 2.8 months; HR = 0.43;  $P < 0.001$ ) [9]. An exploratory endpoint also included the evaluation of changes in bone turnover marker levels and the rate of progressive disease in bone, defined as unequivocal progression of a pre-existing bone lesion or the appearance of a new bone lesion [10]. Everolimus added to exemestane significantly decreased bone turnover marker levels at 6 and 12 weeks. Moreover, the cumulative incidence rate of progressive disease in bone was lower in the combination arm.

## 5. Novel compounds

Other bone-targeting agents are currently under investigation, although the clinical development of SRC- and C-MET inhibitors is further along. Both have shown important

bone-specific activity in patients with breast or prostate cancer, as well as in preclinical models [11,12].

## 6. Conclusions

A better understanding of the biology of bone metastases is establishing an exciting scenario in the treatment of this disease. This explosion of data has led to a large increase in knowledge and the subsequent introduction of new bone-targeted therapies in daily practice.

## Conflict of interest statement

Jose Perez-Garcia and Eva Muñoz-Couselo have no conflict of interest to declare. Javier Cortés is a consultant for Novartis, Roche, Celgene and declares honoraria (speech) from Novartis, Roche, Celgene, Eisai.

## REFERENCES

- [1] Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004;350(16):1655–64.
- [2] Lipton A, Jun S. RANKL inhibition in the treatment of bone metastases. *Curr Opin Support Palliat Care* 2008;2(3):197–203.
- [3] Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 2005;23(22):4925–35.
- [4] Aapro M, Saad F, Costa L. Optimizing clinical benefits of bisphosphonates in cancer patients with bone metastases. *Oncologist* 2010;15(11):1147–58.
- [5] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377(9768):813–22.
- [6] Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29(9):1125–32.
- [7] Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28(35):5132–9.

- 
- [8] Hussein O, Tiedemann K, Murshed M, et al. Rapamycin inhibits osteolysis and improves survival in a model of experimental bone metastases. *Cancer Lett* 2012;314(2):176–84.
- [9] Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366(6):520–9.
- [10] Gnant M, Baselga J, Rugo HS, et al. Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2. *J Natl Cancer Inst* 2012;105(9):654–63.
- [11] Saad F, Lipton A. SRC kinase inhibition: targeting bone metastases and tumor growth in prostate and breast cancer. *Cancer Treat Rev* 2010;36(2):177–84.
- [12] Smith DC, Smith MR, Sweeney C, et al. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. *J Clin Oncol* 2012;31(4):412–9.