Editorial



# Hypocalcemia in patients with metastatic bone disease treated with denosumab

**André Mansinho[1*], Arlindo R Ferreira[1,2*], Luís Costa[1,2]**

[1]Oncology Division, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, 1649-028 Lisbon, Portugal; [2]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, 1649-028 Lisbon, Portugal

*These authors contributed equally to this work.

*Correspondence to:* Luís Costa. Serviço de Oncologia, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, 1649-028 Lisbon, Portugal. Email: luiscosta.oncology@gmail.com.

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Bone stands out as the most frequently affected distant site for metastatic disease, leading to significant patient morbidity, loss of autonomy, decrease in quality of life and increased societal costs. Frequent consequences of metastatic bone disease include pain, hypercalcemia, pathologic fracture, and myeloid compression, collectively referred as skeletal related events (SRE). Bone targeted agents (BTA), such as zoledronic acid (ZA) and denosumab, changed significantly this panorama by delaying time to first and subsequent SRE. These novel agents that fundamentally target bone microenvironment and are thus often referred as BTA, have the merit to be effective in reducing SREs, but also to be the one first class of agents to specifically target the medium influencing cancer outcomes. Such effect is achieved through the disruption of osteoclast activity, either by the direct and specific cytotoxic action of bisphosphonates to osteoclasts or by shutting down RANKL, the most potent activator of osteoclasts, using denosumab. This comes however at a price, briefly, increased frequency of hypocalcemia, a rare jaw lesion referred as osteonecrosis of the jaw (ONJ); and, in some patients, decreased renal function (usually associated with IV bisphosphonates, namely ZA).

Although by different mechanisms, these antiresorptive agents reduce skeletal calcium release into circulation, thus resulting in hypocalcaemia. As recently shown by Body and others, hypocalcemia is more frequent with denosumab than ZA for every tumor type (1,2). This effect is mostly due to the fact that RANKL inhibitors are more potent at reducing bone turnover, consequently reducing the release of calcium into circulation; on the other hand, this also explains the higher efficacy of RANKL inhibitors at reducing SREs in solid tumors (3) [how denosumab and ZA compare in patients with multiple myeloma is still a matter of debate (4)]. Oncologists should however consider that the risk of hypocalcemia can be controlled and is reversible, making this a small price to pay when put into perspective of the clinical advantage at preventing SREs. In this study the risk of developing hypocalcemia was 40% lower in patients treated with denosumab who reported taking calcium/vitamin D supplements at any time during the study, which highlights the importance of adhesion to calcium supplementation in patients receiving denosumab. Besides inadequate intake of vitamin D and calcium, parathyroid dysfunction or impaired renal function, both having a critical role in the phosphocalcic metabolism, further add to this risk and should therefore be in the mind of treating oncologists.

Extensive osteoblastic metastases have also been associated with hypocalcemia independently of treatment with BTAs; BTAs further add to this risk. Prostate cancer is well-known for causing osteoblastic bone metastasis, which could explain why it has a higher incidence of hypocalcemia. However, in this particular analysis, radiographic pattern of bone metastases did not modulate the risk of hypocalcemia. As a matter of fact, blastic lesions were associated with hypocalcemia in the univariate analysis, but not in the multivariate analysis. The granular use of other variables,

as markers of bone metabolism that more closely inform the biochemical events of bone metabolism, might explain this empirical discrepancy and why blastic lesions no longer associate with hypocalcemia when controlling for markers of bone metabolism. Seen from another angle, this might constitute an additional argument in favor of the use of markers of bone metabolism to stratify for the risk of hypocalcemia. However, until an updated consensus is reached in this matter (5), radiographic pattern of bone metastases should be used as an empirically risk factor for the development of hypocalcemia in the context of treatment with BTAs.

In a small retrospective chart review assessing the risk of hypocalcemia in patients receiving ZA, Hanamura and colleagues (6) identified other risk factors for hypocalcemia, as lower adjusted serum calcium concentrations at date of initiation of ZA and concurrent administration of corticosteroids. It is known that corticosteroids suppress intestinal calcium absorption, depress vitamin D activity and reabsorption of calcium in renal tubules, therefore inducing hypocalcemia. Of note, the majority of patients who have metastatic castration resistant prostate cancer (mCRPC) receive steroids concurrently with taxanes or abiraterone thus being a common situation in these patients.

Besides hypocalcemia, ONJ is also a matter of clinical attention. While the proportion of patients with hypocalcemia tends to be highest in the first administrations, recent data highlights the added risk of ONJ with cumulative exposure to denosumab, as to other BTAs (7). In patients planned to start on BTAs, treating physicians should consider a full dental examination and any eventual oral health intervention should be performed before the initiation of BTAs. Furthermore, patients should be aware of the importance of continued oral health, to report oral health symptoms and avoid major oral health interventions (as dentoalveolar surgery) during treatment with BTAs. Finally, frequent clinical assessment of oral mucosa integrity should also be a priority, especially in case of long-term treatment.

Over past years, several studies tested the role of de-escalated regimens of ZA and denosumab in patients with breast cancer and bone metastases. In these studies, patients with low levels of bone remodeling markers at baseline or after completing at least 3 months of BTAs at conventional dose had their BTA de-escalated from every 3–4 weeks to every 12 weeks. In a pooled analysis of these studies, therapy de-escalation did not show any detrimental effect in the rate of on-study SREs or pain (8). This might translate into relevant gains in patients' safety (by reducing rates of hypocalcemia and ONJ), quality of life (by reducing the need for in-hospital treatments) and health costs (both deriving from drug use and management of side effects).

Despite not preventable, risk for hypocalcemia can be managed by closely monitoring those with risk factors for hypocalcemia (especially during the first 6 months of therapy), by supplementing patients with calcium and vitamin D, by including patients in dose de-escalation regimens (at least those with primary breast cancer) and by selecting for BTA therapy only those patients with well-established benefit (as by saving non-CRPC with bone metastasis from BTAs).

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