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EXPERT OPINION

Calcitriol: a better option than vitamin D in denosumab-treated patients with kidney failure?

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Denosumab has been proven to be at least as effective with respect to zoledronic acid in preventing skeletal-related events in patients with bone metastases from solid tumors. Although denosumab can be considered to have a more favorable toxicity profile compared to zoledronic acid in terms of kidney toxicity and flu-like symptoms, hypocalcemia is twice as frequent with denosumab. Importantly, denosumab is not metabolized by the kidney and it may be employed even in patients with severe kidney failure. Like zoledronic acid, denosumab is administered with oral calcium and vitamin D. As conversion of vitamin D to its active form is progressively impaired with a creatinine clearance < 70 ml/min, we speculate that calcitriol may be a better option than vitamin D in denosumab-treated patients with impaired kidney function.

Keywords: bone metastasis, calcitriol, denosumab, zoledronic acid

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1. Editorial

About two-thirds of patients with breast and prostate cancer and about one-third of patients with thyroid, kidney and lung cancer develop bone metastases [1]. Differently from lung or liver metastases from solid tumors such as colo-rectal, testicular or kidney cancer, bone metastases are rarely amenable to a curative approach, even in case of a solitary metastasis, and their management is mostly palliative [2]. The grim prognosis of metastatic bone cancer is also associated with substantial morbidity, due to a number of well-known 'skeletal-related events' (SREs), such as fractures, hypercalcemia, pain and spinal cord compression [3]. These events can have a tremendous impact on patients' quality of life and self-sufficiency, with a considerable economic burden for society in terms of hospital admissions, radiotherapy sessions and surgery procedures. Bisphosphonate agents have met a compelling need in oncology, as several agents of this class have been associated with a statistically and clinically meaningful prolongation of time to first SRE in patients with solid tumors and multiple myeloma in several large, randomized controlled trials [3]. In particular, zoledronic acid (ZOL), a nitrogen-containing bisphosphonate, has the most appealing pharmacodynamic profile. Besides binding to the hydroxyapatite crystals of the bone and preventing both their growth and their dissolution, ZOL directly suppresses osteoclast activity by inhibiting prenylation of small GTPases involved in the cellular processes required for osteoclastic bone resorption [4]. Denosumab is a novel, fully humanized monoclonal antibody directed against the ligand (L) of the receptor activator of nuclear factor kappa B (RANK), thus preventing its interaction with RANK. Although a number of resident and transient host cells in the bone marrow, including platelets, immune and mesenchymal stem cells, and a number of soluble and nonsoluble factors, including transforming growth factor beta (TGF-beta), parathormone-related peptide (PTH-rP), bone morphogenetic proteins are involved

at different levels of the multi-step process leading to cancer-mediated bone resorption, a large body of evidence suggests that the most prominent role is played by osteoblast–osteoclast interaction mediated by RANK and RANK-L, which explains the clinical effectiveness of denosumab [3]. In fact, denosumab was superior to zoledronic acid in prolonging time to first on-study SRE in 2046 patients with breast cancer [5] (hazard ratio 0.82; 95% CI 0.71 – 0.95) and in 1904 patients with castration-resistant prostate cancer [6] (hazard ratio 0.82; 95% CI 0.71 – 0.95). In breast cancer patients, denosumab also significantly delayed the onset of moderate/severe pain and provided meaningful improvement in quality of life with respect to ZOL [7]. Furthermore, in 1774 patients with multiple myeloma or advanced solid tumors (excluding breast and prostate cancer) metastatic to the bone, denosumab was statistically noninferior to ZOL in prolonging time to first SRE (hazard ratio 0.84; 95% CI 0.71 – 0.98) [8].

2. Expert opinion

Apart from similar rates of osteonecrosis of the jaw reported with either denosumab or ZOL, the toxicity profile of denosumab and ZOL exhibits interesting differences. In breast cancer patients, ZOL caused acute phase reactions (27.3 vs 10.4%) and adverse events potentially associated with renal toxicity (8.5 vs 4.9%) more frequently than denosumab [5]. If data from the two separate Phase III trials in patients with prostate cancer [6] and in patients with multiple myeloma and other solid malignancies (except for prostate and breast cancer) [8], respectively, are pooled together, acute phase reactions were more frequent in the ZOL arm with respect to denosumab arm, while incidence of adverse events potentially associated with renal toxicity was similar in both arms. If patients enrolled in the mentioned Phase III trials on denosumab vs ZOL [5,6,8] are grouped together in a sample of 5677 patients, incidence of hypocalcemia of any grade was double in patients treated with denosumab vs ZOL (18 vs 9%), while severe hypocalcemia (corrected serum calcium less than 7 mg/dl) occurred in 3.1% of patients treated with denosumab and in 1.3% of patients treated with ZOL [9]. No fatal events were related to denosumab-induced hypocalcemia, but severe hypocalcemia could require hospitalization for administration of intravenous calcium gluconate. In our view, asymptomatic hypocalcemia is also to be treated and prevented, as it is able to delay denosumab administration, with an unknown effect on its efficacy.

Denosumab was not assessed in patients with a creatinine clearance inferior to 30 ml/min, who were excluded from the Phase III trials [5,6,8]. One study, conducted in 54 patients with a varying degree of kidney failure receiving a single dose of 60 mg denosumab, suggested that denosumab could be safely administered also in patients with severe kidney failure, on the condition that adequate supplementation of calcium and vitamin D and adequate management of secondary hyperparathyroidism were provided [10]. This study was conducted with a single dose of 60 mg denosumab, so no data are available on the effect of multiple administrations of the standard 120 mg dose. If we admit the possibility that, unlike ZOL, denosumab may be employed even in patients with severe kidney failure, it must be observed that vitamin D supplementation may be a less effective supportive therapy in these patients, as its conversion to its active form via 1-alpha-hydroxylation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol is progressively impaired in patients with a creatinine clearance below 70 ml/min [11]. In these patients, the positive effects on calcium homeostasis of oral calcitriol, which is an active form of vitamin D which does not require 1-alpha-hydroxylation by the kidney, have been established for decades [12], with recent reports indicating even an effect on survival in patients with a wide degree of kidney failure [13]. Furthermore, one study conducted in 32 patients with early renal failure concluded that calcitriol could contribute to the efficiency of the homeostatic mechanisms controlling serum calcium, via enhanced renal tubular reabsorption of calcium in patients with hypocalcemia and reduction of tubular reabsorption of calcium in patients with mild hypercalcemia [14]. This finding suggests that calcitriol should not increase the risk of hypercalcemia, provided calcium serum levels are adequately monitored and calcitriol doses adjusted throughout the course of treatment. Taken all of these considerations into account, we hypothesize that the use of calcitriol may be advantageous in combination with denosumab in at least two different experimental settings: in cancer patients with a creatinine clearance inferior to 30 ml/min and in those with mild to moderate kidney failure with recurrent hypocalcemia. The clinical efficacy of denosumab remains to be defined in the former group, while in the latter group, which represents a significant proportion of patients considering that approximately 12% of patients with solid tumors are reported to have a creatinine clearance < 60 ml/min [15], calcitriol may help to manage cases with refractory or severe hypocalcemia, which may even preclude denosumab continuation. In this regard, it must be noted that in the Phase III trials, up to 33% of patients who experienced severe hypocalcemia had recurrent events in spite of oral supplementation of calcium and vitamin D [9]. We suggest calcitriol to be tested at a starting dose of 0.25 mcg daily and increased up to 1 mcg daily in association with standard doses of oral calcium.

In conclusion, denosumab-induced hypocalcemia presents several important aspects which require to be tackled in an experimental setting. It is our opinion that calcitriol may be advantageous to treat or prevent hypocalcemia in a subset of patients receiving denosumab. We warrant further investigation to validate this hypothesis.

Declaration of interest

G Di Lorenzo is a member of advisory boards for Sanofi-Aventis and Pfizer, and has served as a consultant for Teva. None of the other authors have any competing interests to disclose. No funding was received in preparation of this article.

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