Editorial

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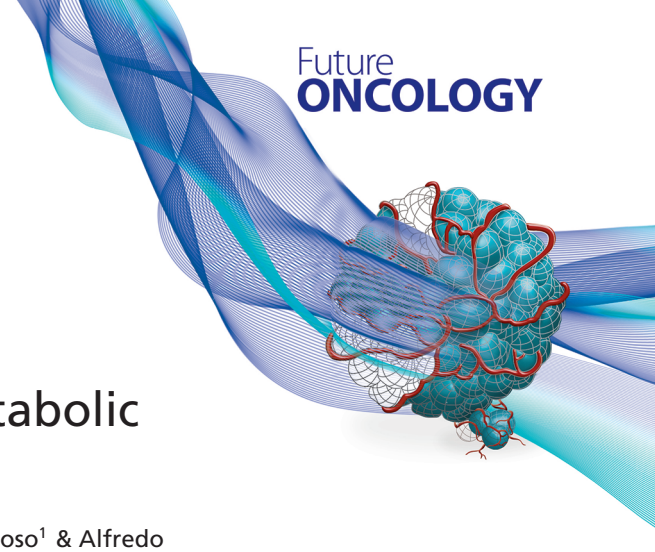

Excess of second tumors in denosumab-treated patients: a metabolic hypothesis

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"Since the increase in second malignancies observed in patients treated with denosumab compared with zoledronic acid seems to be proportional to the augmented rate of hypocalcemia, it is plausible to infer that secondary hyperparathyroidism could play a role in favoring the excess of second tumors seen in patients treated with denosumab."

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Denosumab and zoledronic acid are the most frequently used bone resorption inhibitors to prevent symptomatic skeletal events (SSE) in cancer patients with bone metastases. Denosumab is a fully human monoclonal antibody that binds to RANK-L and inhibits osteoclast maturation. Zoledronic acid is a bisphosphonate that induces apoptosis of mature osteoclasts.

In May 2018, prescribers of these drugs were warned about the increased incidence of second tumors in denosumab-treated patients. This alert was based upon the results of four Phase III studies that compared the efficacy of denosumab and zoledronic acid in bone metastatic patients suffering from castration-resistant prostate cancer, breast cancer, different advanced cancers (mostly lung cancer) and multiple myeloma [1–4].

In all these studies, denosumab, administered subcutaneously at the dose of 120 mg every month, was superior to zoledronic acid in terms of reduction of the risk of adverse skeletal-related events (defined as the occurrence of any among pathologic fracture, spinal cord compression, necessity for radiation or surgery to bone), due to a more potent inhibition of the osteoclast activity. However, in patients randomized to receive denosumab there was a small increased proportion of second malignancies (ranging from 0.5 and 2.2%) comparing to patients who received zoledronic acid (0.3–1%).

Since the greater frequency of malignancies linked to denosumab therapy was observed in three out of four trials [1,3,4], this observation seems not to be casual. Therefore, we have wondered what could be the possible mechanisms responsible for this phenomenon.

The onset of second neoplasms could be related to the denosumab dose & schedule

Denosumab induces RANK-L inhibition and blocks osteoclast maturation. It is unlikely, however, that this mechanism *per se* can favor progression and diffusion of cancer cells. Several preclinical *in vivo* and *in vitro* studies, in fact, demonstrated that RANK-L expression promotes tumor cell migration, invasion and angiogenesis [5,6]. Moreover, cytokines and growth factors, produced by tumors, stimulate RANK-L and may reduce osteoprotegerin and increase T-regulatory cells, thus favoring tumor growth in bone microenvironment [7]. By contrast, several RANK-L-targeting drugs, including denosumab, led to reduction in skeletal tumor growth, cell proliferation and increase cell apoptosis and survival in mice bearing different tumor types [8]. On these bases, RANK-L inhibition can exert a protective role against progression and diffusion of cancer cells.

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Noteworthy, denosumab, at the subcutaneous dose of 60 mg every 6 months, was also tested against placebo in women receiving adjuvant aromatase-inhibitor therapy for breast cancer [9] and in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer [10], with the aim to prevent bone mass loss and fractures. In these studies, denosumab administration was not associated to an excess of second neoplasms (proportion of second malignancies 1.5 vs 1.1% and 5 vs 5% in denosumab and placebo arms in the two studies, respectively).

Although the settings are different, one hypothesis is that the dose and schedule of denosumab could have had a role in favoring second neoplasms, in other words the deeper and more prolonged was the osteoclast inhibition the greater was the risk of second malignancies. An early effect of bone resorption inhibition is hypocalcemia. So the lower and delayed dose of denosumab administration in the nonmetastatic studies led to a less proportion of hypocalcemia with respect to the higher dose adopted in metastatic patients [9,10].

PTH elevation as a consequence of denosumab-induced hypocalcemia may promote the appearance of second tumors

Serum calcium level is a master regulator for PTH incretion, resulting in an increased release of the hormone in presence of hypocalcemia. PTH may have promotional activity of cancer progression [11]. PTH, in fact, has an amino-terminal sequence homology with PTHrP, a hormone that notoriously stimulates cell growth and inhibits apoptosis in different cell types, and both PTHrP and PTH bind to the same receptor (PTH1R) with similar affinity, resulting in equal responses in terms of quality and quantity. PTH1R belongs to the G-protein-coupled receptor family and is placed upstream of a signal cascade involved in cell survival, antiapoptotic activity and migration [11]. PTHrP stimulates angiogenesis, inflammation and *Wnt* pathway in osteosarcoma cells [12], it promotes cell cycle and migration of colon cancer cells [13] and confers antiapoptotic stimuli to renal cancer cells [14]. Furthermore, the stimulating effect of PTHrP on tumor proliferation and progression is not limited to these neoplasms, so the finding that many cancers express PTHR1 suggests a direct role of PTH in promoting the clonal growth of transformed neoplastic cells [15]. It is pertinent mentioning that in a *post hoc* analysis of the registrative trial of zoledronic acid versus placebo in bone metastatic prostate cancer patients, PTH elevation was a negative prognostic factor in zoledronic acid treated patients [16].

Unfortunately, in the aforementioned Phase III studies of denosumab administration, both in nonmetastatic and metastatic setting, PTH was not measured. However, provided the strong inverse correlation between PTH and serum calcium concentrations, the rate of hypocalcemia could be considered a valid surrogate of PTH elevation.

As mentioned before, it is interesting to note that in the nonmetastatic studies [9,10] no difference in hypocalcemia (all grades) between denosumab and placebo arms was observed (0.1 vs 0.1% [9] and 0.1 vs 0% [10]). Conversely in the metastatic studies, denosumab was more frequently associated to hypocalcemia than zoledronic acid due the higher doses administered and, intriguingly, in patients randomized to denosumab there was an increased proportion of second malignancies.

Analyzing the data of single studies, it should be noted that in the three studies in which the frequency of severe hypocalcemia (grade 3–4) was considerably higher in the denosumab versus zoledronic acid arm (5 vs 1% [1], 2.3 vs 1% [3] and 4 vs 2.6% [4]) there was also an increased frequency of second malignancies (2 vs 1% [1], 0.6 vs 0.3% [3] and 2.2 vs 0.8% [4]). This was not the case in the study involving breast cancer [2] in which the similar frequency of severe hypocalcemia in both arms (1.6 vs 1.2%) was associated with a same proportion of second malignancies (0.5 vs 0.5%). The higher rates of hypocalcemia (and consequently second malignancies) were observed in the studies in which patients with prostate cancer and multiple myeloma were involved. This phenomenon could be explained by osteoblast nature of bone metastases from prostate cancer leading *per se* to calcium entrapment in bone (the so-called bone hunger syndrome) [17], and renal impairment that often follows multiple myeloma; both these conditions favor the occurrence of hypocalcemia after bone resorption inhibitors.

Conclusion

Since the increase in second malignancies observed in patients treated with denosumab compared with zoledronic acid seems to be proportional to the augmented rate of hypocalcemia, it is plausible to infer that secondary hyperparathyroidism could play a role in favoring the excess of second tumors seen in patients treated with denosumab. A *post hoc* analysis exploring the correlation between second malignancies and drug-induced hypocalcemia in the above-mentioned randomized clinical trials could provide support to this hypothesis. If confirmed, our assumption may imply that calcium and PTH should be regularly monitored during intravenous administration of denosumab and calcium and vitamin D supplementation should target PTH elevation [18].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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