Management of the side-effects of intravenous bisphosphonates: targeting the serum parathyroid hormone elevation

In their recent review article, Tanvetyanon and Stiff [1] pointed out that hypocalcemia is a frequent side-effect of intravenous bisphosphonates. This adverse event is usually mild and exceptionally symptomatic, with the principle risk factors being pre-existing hypovitaminosis D, previous parathyroid surgery and intestinal resections. A direct consequence of hypocalcemia is secondary hyperparathyroidism and its associated sequelae, which underlines the importance of correcting the calcium imbalance. Secondary hyperparathyroidism, however, may persist even when the hypocalcemia is corrected. Parathyroid hormone (PTH) elevation may impair the efficacy of bisphosphonates. PTH is a potent stimulator of osteoclast activity [2], in addition it favours the production of cytokines and growth factors in the bone microenvironment [2] that may stimulate tumor growth thus perpetuating the vicious cycle. Perhaps more importantly, PTH may have promotional activity of cancer progression [3]. PTH, in fact, has an amino-terminal sequence homology with parathyroid hormone related peptide (PTHrP), a hormone that stimulates cell growth and inhibits apoptosis in different cell types, and both PTHrP and PTH bind to the same receptor (PTH1R) with the same affinity that results in responses of the same quality and quantity [2]. The finding that many cancers express PTH1R suggests a direct role of PTH in tumor progression and cell proliferation [3]. At the last meeting of the American Society of Clinical Oncology a retrospective and exploratory analysis on the outcome effect of PTH elevation after zoledronic acid administration in more than 1000 bone metastatic cancer patients randomized in the three registrative zoledronic acid studies has been presented [4].

The results showed that the PTH increase in the first 3 months of zoledronic acid treatment was associated with an increased risk of death in overall population and in the prostate and breast cancer subsets and to an increased risk of disease progression in bone in the prostate cancer subgroup. A potential confounder in this analysis is vitamin D deficiency by itself. Vitamin D exerts potent antiproliferative effects on hyperproliferative and normal cells in bone, B and T lymphocyte population, skin, intestine etc. and vitamin D deficiency has been associated with increased risk of colon, breast and prostate cancer [5]. Thus, the elevated PTH levels might be an indirect marker of insufficiently treated vitamin D deficiency, signifying decreased antiproliferative potential. Noteworthy, prostate cancer patients with normal PTH levels at baseline showed a significant survival advantage after zoledronic acid administration. Even though caution should be adopted in generalizing the results coming from an unplanned and retrospective analysis, these data suggest that secondary hyperparathyroidism may be a newly recognized side-effect of intravenous bisphosphonates that need to be corrected since it can potentially impair the efficacy of these drugs.

These data have several implications: (1) 25(OH)D and PTH should be regularly monitored during intravenous administration of bisphosphonates; (2) calcium and vitamin D supplementation should target PTH elevation and not only calcium levels; (3) the efficacy of intravenous bisphosphonates in the management of bone metastatic patients could potentially be improved if secondary hyperparathyroidism is effectively counteracted.

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