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Bisphosphonate or RANK-L inhibitor for tumour-induced hypercalcaemia?

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Dear Editor,

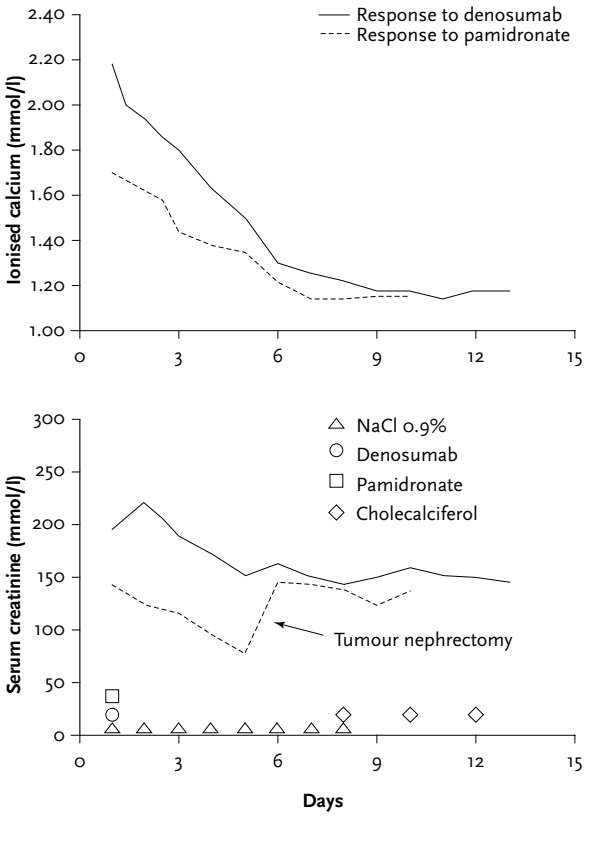
We would like to share our experience with a new treatment approach for tumour-induced hypercalcaemia complicated by renal failure in a patient with renal cell carcinoma (RCC). About 10% of RCCs produce humoral factors that may cause severe hypercalcaemia.[1] The most commonly secreted factor is parathyroid hormone-related peptide (PTH-rp), but cytokines such as IL-6, IL-1, prostaglandin E2, TNFα and TGFα and TFGβ have also been associated with RCC-related hypercalcaemia.[1-3] The underlying mechanism is enhanced osteoclast activity induced by stimulation of the receptor activator of nuclear factor-κ ligand (RANK-L), a key protein in the upregulation of osteoclast formation and activity.[1,2]

Recently, monoclonal antibodies to RANK-L have become available for the treatment of osteoporosis.[4] These antibodies are cleared by the reticulo-endothelial system. Therefore, RANK-L inhibitors such as denosumab might be of value in patients with renal failure, i.e. circumstances where bisphosphonates are relatively contraindicated.[5]

When a 48-year-old man with a recent diagnosis of RCC presented with severe hypercalcaemia and renal failure, denosumab was considered to be the agent of choice. Blood testing revealed a serum creatinine of 191 μmol/l (calculated glomerular filtration rate (GFR) 31 ml/min), ionised calcium (Ca^{2+}) 2.18 mmol/l, PO_4 1.11 mmol/l, PTH <0.3 pmol/l, PTH-rp 7.1 pmol/l (upper normal limit: 2.0 pmol/l), alkaline phosphatase 94 U/l, 25-OH vitamin D 14 nmol/l, and 1.25-OHD 59 pmol/l. A PET-CT showed an FDG-positive tumour in the right kidney, pathological uptake in mediastinal and supraclavicular lymph nodes, but no signs of bone metastases.

The patient was treated with NaCl 0.9% intravenously at a rate of 4 litres/24 hours, and a single dose of denosumab 60 mg, subcutaneously, on the day of admission. A rapid decline in serum calcium and a partial recovery of renal function was observed (*figure 1*). After one week cholecalciferol 50,000 IU was given three times to correct a concomitant vitamin D deficiency. Two weeks later the patient again presented with severe hypercalcaemia (Ca^{2+} 1.71 mmol/l, calculated GFR 45 ml/min, 25-OHD 38

Figure 1. *Course of serum ionized calcium and creatinine levels in response to forced hydration and a single dose of denosumab 60 mg, administered on the first day of admission. A second hypercalcaemic episode was treated with a similar hydration scheme plus a single dose of pamidronate, 90 mg intravenously.*



nmol/l). Upon readmission he was treated with NaCl 0.9%, 4 litres/24 hours and a single dose of pamidronate, 90 mg intravenously. The speed of decline in serum calcium was somewhat less to that induced by denosumab (*figure 1*). On the 6th day of admission tumour nephrectomy was performed. The observations in this case suggest that denosumab is a potent treatment strategy for humoral hypercalcaemia. It may become the preferred agent in case of renal failure.

REFERENCES

1. Pepper K, Jaowattana U, Starsiak MD, et al. Renal cell carcinoma presenting with paraneoplastic hypercalcemic coma: a case report and review of the literature. J Gen Intern Med. 2007;22:1042-6.
2. Yin JJ, Pollock CB, Kelly K. Mechanisms of cancer metastasis to the bone. Cell Res. 2005;15:57-62.
3. Motellón JL, Jiménez FJ, de Miguel F, et al. Relationship of plasma bone cytokines with hypercalcemia in cancer patients. Clin Chim Acta. 2000;302:59-68.
4. Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res. 2005;20:2275-82.
5. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008;74:1385-93.