A RANKL Wrinkle: Denosumab-Induced Hypocalcemia

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Abstract The human monoclonal antibody denosumab inhibits osteoclast-mediated bone resorption by binding to receptor activator of nuclear factor κ B ligand (RANKL), which is upregulated by tumor cells. Denosumab is indicated to prevent skeletal-related events (SREs) from osteoporosis and metastatic bone disease. We report a case of denosumab-induced hypocalcemia to highlight potential toxicity and treatment considerations. A 66-year-old man with prostate cancer, small cell lung cancer, and bone metastases presented with fatigue, weakness, and muscle spasm. Sixteen days prior, he received cycle 6 of cisplatin and etoposide, leuprolide, and denosumab (120 mg subcutaneously). His examination demonstrated a slight resting tremor, normal strength, and negative Chvostek sign. Laboratory analysis revealed hemoglobin, 8.0 g/dL; total calcium, 5.2 mg/dL (pre-denosumab, 8.9 mg/dL); and magnesium, 0.7 mg/dL. He initially received two units packed red blood cells, intravenous calcium and magnesium, and vitamin D. During his hospitalization, he required multiple doses of intravenous and oral calcium, magnesium, and vitamin D. Despite ongoing oral supplementation, his post-discharge serum calcium fluctuated significantly, requiring close monitoring and

frequent dose adjustments. Denosumab's unique antiresorptive properties yield fewer SREs. The trade-off is increased hypocalcemia risk, which may be severe and require aggressive, prolonged supplementation and monitoring.

Keywords Adverse drug reaction · Cancer · Hypocalcemia · Denosumab · Toxicology

Introduction

Denosumab is a human IgG₂ monoclonal antibody approved in 2010 to prevent skeletal-related events (SRE) in postmenopausal women at risk for osteoporosis (as Prolia[®]) and in patients with solid tumor bone metastasis (as Xgeva[®]) [1–4]. Denosumab prevents bone destruction by mimicking the action of naturally occurring osteoprotegerin, which binds to and inhibits receptor activator of nuclear factor kappa B ligand (RANKL) [5]. Osteoblasts release RANKL, which binds to receptors on both osteoclast precursors (to stimulate their maturation), and mature osteoclasts (to increase their activity, attachment to bone, and lifespan). RANKL is upregulated in postmenopausal women due to estrogen decline and in various malignancies due to tumor-secreted growth factors [3, 6]. Increased osteoclast activity, excess bone resorption, and decreased bone density contribute to an increased SRE rate. By binding to RANKL and preventing its binding to the RANK receptor, denosumab limits excessive bone resorption and decreases fracture risk.

Denosumab contributes to lower SRE rates compared to the bisphosphonate zoledronic acid (ZA), but the incidence of hypocalcemia from denosumab in cancer patients ranges from 0.1 to 12.8 % [5, 7–14]. We report a case of denosumab-induced hypocalcemia to highlight the unique toxicity and treatment considerations of this novel agent.

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Case Report

A 66-year-old man with prostate cancer, small cell lung cancer, bone metastasis, and chemotherapy-associated, transfusion-dependent anemia presented with fatigue, weakness, and intermittent muscle spasms. Sixteen days prior, he received cycle 6 of cisplatin and etoposide. At this time, he also received his first dose of denosumab (120 mg SC). Initial vital signs were blood pressure, 157/75 mmHg; pulse, 78 beats/min; respirations, 16/min; temperature, 97.7 °F (36.5 °C); oxygen saturation, 100 %. His presenting examination was remarkable for a slight resting tremor and negative Chvostek sign. Laboratory analysis included hemoglobin, 8.0 g/dL; total serum calcium (SCa), 5.2 mg/dL (pre-denosumab SCa, 8.9 mg/dL); albumin, 4.0 g/dL; and creatinine, 1.9 mg/dL (estimated glomerular filtration rate (eGFR) 35.6 mL/min/1.73 m²; baseline creatinine 1.5 mg/dL, eGFR 50.7 mL/min/1.73 m²). An ECG showed normal sinus rhythm and QTc of 456 ms. He received a red blood cell transfusion and calcium gluconate 2 g intravenously, increasing his SCa to 5.6 mg/dL. Administration of calcium gluconate 3 g intravenously and calcitriol 0.5 µg orally, further raised his SCa to 6.5 mg/dL (ionized calcium, 0.86 mg/dL). His serum magnesium was 0.7 mg/dL (baseline unavailable), serum phosphorus was 4.7 mg/dL (baseline 3.7 mg/dL), and intact parathyroid hormone (PTH) was 167 pg/mL (baseline unavailable; range 15–75 pg/mL). He was admitted for telemetry.

Over the first 24 hours, he received multiple doses of calcium (total of 16 g intravenous calcium gluconate and 2.5 g oral

CaCO₃; 2.5 g of CaCO₃ contains 1 g elemental calcium), raising his calcium to 8.4 mg/dL. Concurrently, he received multiple doses of magnesium (total of 8 g intravenous MgSO₄ and 400 mg oral MgO), which raised his magnesium to 1.9 mg/dL. Repeat ECG revealed normal sinus rhythm with shortening of the QTc to 433 ms. A serum 25-OH-vitamin D of 30.8 ng/mL (baseline 30.1 ng/mL; range 30–80 ng/mL) prompted administration of ergocalciferol 50,000 units orally four times daily, cholecalciferol 5000 units orally once, and calcitriol 0.25 µg orally daily (initiated on hospital day 3). By day 4, he was stabilized with oral supplementation and discharged on cholecalciferol 1200 units daily, CaCO₃ 6.25 g (2.5 g elemental calcium) four times daily, calcitriol 0.25 µg daily, and MgO 400 mg twice daily. As an outpatient, his SCa continued to fluctuate, requiring close monitoring and frequent oral calcium supplementation dose adjustments (Fig. 1).

Discussion

Denosumab and ZA are recommended for cancer patients with evidence of bone destruction due to bone metastasis [5]. Denosumab was more efficacious than ZA in reducing the incidence of and delaying time to SRE [15]. Greater tolerability, subcutaneous route, and the absence of nephrotoxicity have contributed to wider denosumab use. However, hypocalcemia risk appears increased with denosumab. In a review and pooled analysis of 8990 patients, the

Fig. 1 Serum calcium trend post-denosumab administration

incidence of all-grade (SCa <8.0 mg/dL) and high-grade (SCa <7.0 mg/dL) hypocalcemia was 5.2 and 2.0 % respectively [5]. Compared to controls receiving either placebo or a bisphosphonate, denosumab was associated with an increased risk of developing all-grade (RR 1.93) and high-grade hypocalcemia (RR 4.03).

Pragmatic reports suggest the incidence and severity of denosumab-associated hypocalcemia may be higher. In a cohort of 60 patients with metastatic prostate cancer who received at least one dose of denosumab (120 mg), 42 patients (70 %) developed hypocalcemia, seven (11.6 %) developed high-grade hypocalcemia, and nine (15 %) required hospitalization for intravenous calcium supplementation [4]. In these cases, severe hypocalcemia developed after the first dose in seven patients, with a median time from drug administration to calcium nadir of 25 days (range, 14–106). Median time to recover baseline calcium was 17 days (range, 6–40); four patients never returned to baseline and died of advanced disease within 3 months. Another case report described a 45-year-old man with refractory denosumab-induced hypocalcemia despite aggressive supplementation with 80 g of IV calcium gluconate and 370 g of oral calcium over 15 days [3]. His SCa finally improved after 4 days of hemodialysis, performed with a high calcium bath, indicated for worsening renal insufficiency in the setting of hydronephrosis due to tumor spread. The patient was sent home on hospice and died 3 weeks later.

Patients with chronic kidney disease (CKD) are at greater risk of developing hypocalcemia, likely due to CKD-associated secondary hyperparathyroidism, which places greater dependence on PTH-mediated bone resorption for maintenance of SCa. An open-label pharmacokinetics and safety study of a single 60-mg subcutaneous dose of denosumab found an incidence of hypocalcemia of 18.6 % in subjects with varying degrees of renal impairment (defined as a creatinine clearance (Cr Cl) <80 mL/min by Cockcroft-Gault estimation) [15].

Another subset of patients at potential increased risk includes those receiving concurrent treatment with medications that interfere with renal and electrolyte physiology. Our patient was being treated with cisplatin, an alkylating agent whose mechanism of action is largely unknown but is established to cause renal tubular damage resulting in hypermagnesuria, hypomagnesemia, functional hypoparathyroidism, PTH resistance, and hypocalcemia [17]. Hypomagnesemia impairs release of PTH by the parathyroid gland, which can contribute to hypocalcemia. It is likely that cisplatin contributed to the profound hypocalcemia in this patient, who presented with a serum Mg of 0.7 mg/dL.

Denosumab, a monoclonal antibody, is eliminated through an immunoglobulin clearance pathway via the reticuloendothelial system, and has a mean elimination half-life of 25–30 days [16]. Given this pharmacokinetic profile, once denosumab-associated hypocalcemia develops, prolonged

treatment and monitoring requirements should be anticipated. Recall that serum calcium is tightly maintained through the effects of 1,25-dihydroxyvitamin D (active vitamin D₃) and parathyroid hormone (PTH). Low SCa induces PTH release, which enhances the conversion of inactive to active D₃. Active D₃ increases intestinal calcium absorption, decreases renal elimination, and increases osteoclast-mediated bone resorption. Thus, treatment of hypocalcemia is greatly enhanced when vitamin D (both inactive and active forms) is co-administered with calcium supplementation.

Prevention of denosumab-induced hypocalcemia via close monitoring of calcium, vitamin D, PTH, magnesium, phosphate, and kidney function is paramount. The Prolia® package insert warns that hypocalcemia may be exacerbated by the medication [1]. It advises correction of pre-existing hypocalcemia and close monitoring of calcium, magnesium, and phosphorus within 14 days of injection in those patients predisposed to hypocalcemia and disturbances of mineral metabolism. It instructs prescribers to supplement their patients with “calcium 100 mg daily and at least 400 IU vitamin D daily,” while Xgeva® advises to “administer calcium and vitamin D as necessary to treat or prevent hypocalcemia” [2]. Although the package insert warns of a “significant risk” of hypocalcemia in patients with severe renal impairment (Cr Cl <30 mL/min or receiving dialysis), dose adjustments are not recommended. We would advise caution and hypervigilance in patients with or at risk of developing renal insufficiency. As some patients with advanced disease may succumb to comorbid illnesses prior to the recovery of normal calcium levels, consideration must weigh the morbidity potential with end-of-life goals.

Limitations

While the profound hypocalcemia seen in this patient is most consistent with an adverse drug effect due to denosumab, other factors may have contributed. Renal effects of cisplatin, as well as secondary hyperparathyroidism, likely played a role in contributing to this patient’s presentation. Etoposide, in contrast, does not have adverse effects on electrolyte balance or renal function, but likely contributed to the patient’s generalized fatigue, weakness, and anemia on presentation.

Conclusion

Denosumab is a novel human monoclonal antibody that inhibits osteoclast-mediated bone destruction by binding to RANKL. With a long elimination half-life, denosumab can produce a severe, prolonged hypocalcemia requiring hospitalization and aggressive IV calcium and vitamin D supplementation. Preventing this complication via careful baseline

assessment, calcium and vitamin D coadministration, and monitoring, is warranted for all patients treated with denosumab.

Compliance with ethical standard

Conflicts of Interest The authors declare that they have no conflicts of interest.

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