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Severe Hypocalcemia Associated With Denosumab in Metastatic Castration-Resistant Prostate Cancer: Risk Factors and Precautions for Treating Physicians

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Keywords

Denosumab; Hypocalcemia; Metastatic prostate cancer; Osteoclast; RANKL; Skeletal-related event

Introduction

Agents that delay or prevent skeletal complications in metastatic castration-resistant prostate cancer (mCRPC) are valuable treatments in this bone tropic malignancy. Denosumab, a fully human monoclonal antibody against RANKL (receptor activator of nuclear factor κ B ligand) a driver of osteoclast formation, function, and survival, inhibits osteoclast-mediated bone destruction. Treatment with denosumab delays the time to skeletal-related events (SREs) such as pathologic fracture or the need for radiotherapy or surgery to bone and decreases the incidence of SREs. In a randomized, double-blind, noninferiority/superiority trial comparing denosumab to zoledronic acid (ZA) in 1901 patients with mCRPC (trial 20050103), denosumab delayed time to first SRE by 3.6 months (20.7 vs 17.1 months) or 18% compared to ZA (hazard ratio, 0.82; 95% confidence interval, 0.71-0.95; $P = .0002$ for noninferiority, $P = .008$ for superiority).¹ Hypocalcemia resulting from a reduction of homeostatic calcium efflux from bone is a known toxicity of both denosumab and ZA.²⁻⁴ In the denosumab 20050103 trial, rates of grade 3 or higher hypocalcemia were 5% with

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denosumab and 1% with ZA. The need for hospitalization and details of severe hypocalcemia were not reported, but no fatal hypocalcemic events were reported.¹ In November 2010, the US Food and Drug Administration (FDA) approved denosumab for the prevention of SREs in patients with bone metastases from solid tumors.

Case Presentation

During a 6-month period after denosumab was approved by the FDA for use in solid tumors, 60 patients with mCRPC at Memorial Sloan Kettering Cancer Center (MSKCC) were treated with denosumab, and 9 developed severe hypocalcemia sufficient to require hospitalization for intravenous calcium replacement. We retrospectively examined the medical records of all 60 patients with mCRPC who received at least 1 dose of denosumab (120 mg) during this time period to determine baseline characteristics, denosumab use, hospitalizations, and laboratory studies at the time of the calcium nadir, as well as medications and comorbidities that may affect calcium metabolism. A waiver of consent was obtained from our Institutional Review Board for this study.

Of the 9 mCRPC patients who required intravenous calcium, 8 required hospitalization. The single patient who was not admitted initiated total parental nutrition with increasing amounts of intravenous calcium as an outpatient and thus was included in this series. Baseline characteristics for these 9 patients as well as those treated with denosumab who did not experience severe hypocalcemia are listed in Table 1. Baseline alkaline phosphatase and prostate-specific antigen (PSA) were notably higher in patients who experienced severe hypocalcemia than those who did not (alkaline phosphatase, 477 U/L vs. 99 U/L; PSA, 194.7 ng/mL vs. 8.2 ng/mL).

The median corrected calcium nadir in those requiring hospitalization was 6.5 (range, 5.0-7.6) mg/dL, and in those who did not require hospitalization it was 8.3 (range, 7.0-9.4) mg/dL. Two of the patients had grade 2 hypocalcemia that was symptomatic; they were thus admitted and intravenous calcium provided. Severity of hypocalcemia was assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.⁵ Overall, the 60 patients who received denosumab were stratified as follows: grade 0, 18 patients (30%); grade 1, 23 patients (38.3%); grade 2, 12 patients (20%); grade 3, 5 patients (8.3%); and grade 4, 2 patients (3.3%).

Severe hypocalcemia occurred after the first dose in 7 of 9 patients and after the second dose in 2 of 9 patients; median time to calcium nadir from administration was 25 (range, 14-106) days. Median time to recovery to baseline calcium levels was 17 (range, 6-40) days in the 5 patients who recovered. The 4 other patients (44%) never recovered to baseline calcium levels, required repeated hospitalizations, and ultimately died of advanced disease within 3 months. Figure 1 highlights one such patient's hospital course. His bone scan before initiation of denosumab is shown in Figure 2A.

Concurrent phosphorus levels were available in 7 of the 9 patients at the time of their calcium nadirs, and 4 (57%) experienced concurrent grade 3 or higher hypophosphatemia. All 9 patients had elevated parathyroid hormone (median, 198 pg/mL; range, 118-353

pg/mL) and low urinary calcium (< 4 mg/dL); normal magnesium levels at the time of calcium nadir were seen in all but one patient.

All patients received the recommended dose of 120 mg of subcutaneous denosumab and were advised to take calcium and vitamin D supplementation. Eight of the 9 patients with severe hypocalcemia reported routine supplementation before beginning denosumab. Median vitamin D (25-hydroxyvitamin D [25-OH]) in those requiring hospitalization was 22.5 (range, 8-68) ng/mL. Three of the 9 patients had values below 20 ng/mL, consistent with deficiency. Medications that could influence calcium levels, such as steroids, chemotherapy, or prior bisphosphonates, are reported in Table 1.

Discussion

This case series of 60 patients with mCRPC treated at MSKCC suggests that denosumab-associated hypocalcemia can be severe. In this analysis, 9 (15%) of 60 patients experienced significant hypocalcemia requiring hospitalization or parenteral supplementation. The need to hospitalize patients for intravenous replacement negatively impacts quality of life, particularly in refractory cases. Identification of potential risk factors for this toxicity is critical to aid in management.

On the basis of this series, advanced disease (ie, osteoblastic disease burden) and vitamin D deficiency appear to be significant risk factors for developing denosumab-associated hypocalcemia. Tumor burden may be reflected by several factors, including alkaline phosphatase. Although alkaline phosphatase is a crude measure of bone metastases burden, it is prognostic of survival and is predictive of SRE risk.⁶⁻¹⁰ In the patients at our center who experienced severe hypocalcemia, baseline alkaline phosphatase was notably elevated—more so than in the other patients in our study or what was reported in the denosumab 20050103 trial or in other randomized phase 3 trials in the metastatic castration resistant disease setting.^{1,6,11} Bone scans were either not quantified¹² or were not available for all 60 patients, and therefore our ability to fully assess bone metastasis burden as a contributing risk factor was limited. Representative scans of those who developed severe hypocalcemia are seen in Figure 2 and are concerning for a superscan.

Extensive osteoblastic metastases have also been associated with hypocalcemia independent of osteoclast-inhibiting agents.¹³⁻¹⁵ Other markers of advanced disease suggest this factor as a possible contributor. PSA was notably higher in these 9 patients, and of them, 7 (77.8%) were receiving chemotherapy, a loose reflection of advanced disease based on treatment patterns in this population at the time. The denosumab 20050103 study required that patients have a minimum life expectancy of 6 months, and the median overall survival was 19.4 months. Thus, patients with very advanced prostate cancer or rapidly progressive disease have not been as well studied in terms of this agent; patients in this case series had more advanced disease as defined by PSA and alkaline phosphatase. Notably, both of these parameters are also independent prognostic risk factors for death, making interpretation of survival in this series challenging.⁸ Although comparing the incidence of hypocalcemia in this small series to those of a large randomized controlled trial (denosumab 20050103) has

its obvious limitations, the higher rates of severe hypocalcemia seen in our patients may in part be attributed to a more advanced CRPC population seen in clinical practice.

Another known risk factor for hypocalcemia is vitamin D deficiency; 3 of the 9 patients had vitamin D 25-OH values lower than 20 ng/mL. Guidelines from the Endocrine Society define vitamin D deficiency as values below 20 ng/mL and insufficiency as values between 20 and 30 ng/mL.^{16,17} In order to mitigate or prevent potential hypocalcemia, vitamin D deficiency should be corrected before initiating denosumab. Vitamin D 25-OH levels may also be monitored during treatment, and appropriate supplementation may be advised. Calcium supplementation is required. Whether patients suspected to be at increased risk for hypocalcemia would benefit from higher doses of calcium prophylactically is uncertain. Notably, although the 9 patients who experienced severe hypocalcemia had relatively normal baseline calcium levels, they were slightly lower than those who did not experience severe hypocalcemia (8.5 vs. 8.9 mg/dL), and 2 of the 9 patients had mild hypocalcemia at baseline. Figure 1 shows calcium levels for a patient who had mild hypocalcemia and secondary hyperparathyroidism before receiving denosumab, a sign that calcium counterregulatory mechanisms were already upregulated.

Comorbidities impairing calcium absorption may have also contributed to the development of hypocalcemia in 3 cases in our series: one patient had a percutaneous endoscopic gastrojejunostomy as he also had a history of treated esophageal cancer; another experienced esophagitis after radiation to a cervical metastasis (the putative mechanism in this patient could also be parathyroid gland insufficiency); a third patient had a history of gastric bypass. Medications such as steroids may impair calcium absorption, and the majority of our patients who experienced severe hypocalcemia were receiving steroids concurrent with taxanes. Another patient receiving cisplatin was hypomagnesemic which may have contributed to the severity of his hypocalcemia as magnesium is known to influence the synthesis and secretion of parathyroid hormone. Prior use of ZA did not appear to be a risk factor, despite its long half-life and retention in bone. The patient depicted in Figure 1 had a history of alendronate therapy for 2 years immediately before the denosumab dose that precipitated severe hypocalcemia. Alendronate has the highest bone-binding avidity of the oral bisphosphonates¹⁸ and may have contributed residual effects.

Severe hypophosphatemia was noted in 57% of patients who developed hypocalcemia. The observed low phosphorus level may be due to the phosphaturic effect of high parathyroid hormone levels induced by hypocalcemia (secondary hyperparathyroidism). Serum phosphorus levels should be checked in all patients presenting with hypocalcemia after denosumab administration. Calcitriol (activated vitamin D) can be useful in correcting both acute hypocalcemia and acute hypophosphatemia, as it accelerates gastrointestinal absorption of calcium and phosphorus and suppresses parathyroid hormone.

When denosumab was studied as a treatment for osteoporosis (at a lower dose and frequency —60 mg every 6 months) in a population with chronic renal insufficiency, serum calcium lower than 7.5 mg/dL or symptomatic hypocalcemia was observed in 29% of patients with a creatinine clearance less than 30 mL/min/1.73 m².¹⁹ Although chronic renal insufficiency is

known to predispose patients to hypocalcemia, it did not appear to be a risk factor in our series.

Conclusion

Tumor burden/advanced disease, vitamin D insufficiency/deficiency, and potentially impaired calcium absorption likely contributed to the profound hypocalcemia associated with denosumab in this case series. Many of the proposed risk factors are readily accessible to the clinician. Hypocalcemia should be corrected before denosumab initiation, and patients with calcium values at the lower limit of normal being considered for potent antiresorptive therapy could be screened for secondary hyperparathyroidism. Additionally, elevated alkaline phosphatase, elevated PSA, and concurrent need for chemotherapy in mCRPC may loosely reflect advanced disease, an apparent risk factor for severe hypocalcemia in this series, and particularly among those who experienced irreversible hypocalcemia. This clinical profile is consistent with a published report of 2 patients with mCRPC and advanced bone disease receiving chemotherapy who also experienced severe, prolonged hypocalcemia after denosumab use.²⁰ Paradoxically, those with advanced disease and high risk for SRE that could benefit from SRE reduction may be the very group at highest risk for severe hypocalcemia with denosumab. Men with mCRPC and extensive bone disease represent a growing population of patients who are living longer as a result of therapeutic advances. Patients with advanced disease and poor prognosis (life expectancy < 6 months) may be less likely to benefit from denosumab, emphasizing the importance of patient selection and identification of potential risk factors. Clinicians should carefully balance the risks of disease with the potential toxicities associated with the very therapies designed to protect and maintain functionality and quality of life.

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Clinical Practice Points

- Bone is the most frequent site of metastatic disease in prostate cancer, which can lead to skeletal-related events (SREs) such as pathologic fracture and cord compression.
- Denosumab is approved by the US Food and Drug Administration for use in solid tumors with bone metastases to prevent or delay SREs such as new fracture and the need for radiotherapy to bone.
- Our case series suggested that a higher prevalence of severe and often prolonged hypocalcemia requiring hospitalization may occur in patients with metastatic castration-resistant prostate cancer in clinical practice. Hypophosphatemia was also commonly identified in cases of severe hypocalcemia.
- Increased disease burden and vitamin D deficiency were discernible risk factors. Patients with albumin-corrected calcium levels in the low normal range may also be at risk.
- Hospitalization for aggressive calcium and vitamin D replacement, calcitriol therapy, and correction of other electrolyte imbalances is encouraged for patients who experience severe hypocalcemia while receiving treatment.

Figure 1.
Hospital Course of A Patient With Severe Hypocalcemia. *Calcium Values Not Corrected for Albumin in the Figure
Abbreviations: H = upper limit of normal range for calcium; L = lower limit of normal range for calcium.

Figure 2.
Representative Bone Scans of Four Patients Who Were Hospitalized For Severe Hypocalcemia

Table 1

Baseline Characteristics of Patients With Metastatic Castration-Resistant Prostate Cancer Receiving Denosumab

Characteristic	Patients Requiring Hospitalization for Hypocalcemia (n = 9)	Patients Remaining Normocalcemic (n = 51)
Age (years)	70 (60-80)	69 (46-89)
PSA (ng/mL)	194.7 (1.1-2470)	8.2 (<0.05-3147)
Gleason score	7 (5-9)	8 (5-9)
Corrected calcium (mg/dL)	8.5 (7.8-9.0)	8.9 (8-9.7)
Alkaline phosphatase (U/L)	477 (65-1387)	99 (37-595)
Creatinine clearance (mL/min/ 1.73 m ²) ^a	79 (26-134)	72 (22-121)
Renal insufficiency (Cr Cl < 60 mL/min/1.73 m ²)	2 (22.2%)	13 (25.5%)
History of radiation to cervical spine, esophagus, or thyroid	2 (22%)	2 (0.4%)
History of gastric bypass, ileal or small bowel resection, or malabsorption disorder	1 (11%)	0 (0%)
History of bisphosphonate therapy ^b	5 (55%)	34 (67%)
Concurrent chemotherapy ^c	7 (77.8%)	13 (25%)
Concurrent steroids	6 (66.7%)	23 (45%)

Data are presented as median (range) or n (%).

Abbreviations: Cr Cl = creatinine clearance; PSA = prostate-specific antigen.

^aCreatinine clearance was calculated by Cockcroft-Gault formula.

^bIncludes oral and intravenous bisphosphonate within 5 years of denosumab administration.

^cOne patient in the hypocalcemic cohort received cisplatin. The remainder were treated with taxanes.