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

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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.

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## 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 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

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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.

**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.
[a]Creatinine clearance was calculated by Cockcroft-Gault formula.
[b]Includes oral and intravenous bisphosphonate within 5 years of denosumab administration.
[c]One patient in the hypocalcemic cohort received cisplatin. The remainder were treated with taxanes.

## 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