Denosumab for the Management of Hypercalcemia of Malignancy in Patients With Multiple Myeloma and Renal Dysfunction

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Clinical Practice Points

- Hypercalcemia and renal dysfunction are common sequelae associated with multiple myeloma and portend poor outcomes.
- Resistance to bisphosphonates and uncertainty regarding dosing in the setting of renal dysfunction could limit the utility of these agents.
- Weight-based denosumab dosing might be a reasonable alternative for patients with multiple myeloma in the setting of recalcitrant hypercalcemia and renal dysfunction; such a strategy might minimize the risk of profound and prolonged hypocalcemia.
- The serum calcium levels should be routinely monitored in all patients receiving denosumab for hypercalcemia of malignancy.

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Introduction

Multiple myeloma is a plasma cell neoplasm that exploits the surrounding stroma to gain a survival and growth advantage.[1] Direct interactions between myeloma cells and stromal cells induce a variety of cytokines (eg, interleukin [IL]-6, IL-10) and growth factors (eg, vascular endothelial growth factor, transforming growth factor-β1). The receptor activator nuclear factor κβ (RANK) pathway is also upregulated, and its activation leads to osteoclast production and bone resorption.[1,2] The clinical manifestations of this process include progressive bone destruction, leading to pathologic fractures, spinal cord compression, and hypercalcemia.[3] Eighty percent of patients with myeloma will experience bone disease, and 1 of 3 patients will have clinically significant hypercalcemia.[3]

Hypercalcemia can complicate the management of myeloma by precipitating dehydration and prerenal azotemia. This metabolic condition often exacerbates renal injury that is already present owing to the production of paraproteins. Thus, 20% to 40% of patients with multiple myeloma will present with some degree of renal insufficiency. Patients with multiple myeloma and stage IV acute kidney injury have shortened survival and mortality of $\leq$ 30% at 2 months.[4]

The standard approach to hypercalcemia of malignancy (HCM) is fluid resuscitation and intravenous bisphosphonate therapy.[5] Although treatment with pamidronate or zoledronic acid has been quite effective, these agents are difficult to use in the presence of acute kidney injury owing to their reliance on renal clearance.[6] As such, these agents can lead to recalcitrant hypocalcemia. Furthermore, clinical trials have often excluded patients with a creatinine clearance of $<$ 30 mL/min.[2,7,8] This lack of data has left practicing clinicians with little guidance for the use of intravenous bisphosphonates in patients with acute kidney injury. Although this is an issue for the management of HCM in general, it has more significance for patients with in multiple myeloma, because treatment with bisphosphonates improves survival.[9]

Denosumab is a humanized antibody targeting the RANK ligand administered subcutaneously and is approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis and the prevention of skeletal-related events (SRE) in patients with solid tumors.[10] Although not currently approved by the FDA for the treatment of HCM, the use of denosumab against HCM makes biologic sense because the RANK pathway is likely the final common mediator of several pathways leading to hypercalcemia.[3] Specifically, multiple myeloma often results in enhanced

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osteoclastogenesis and bone resorption owing to the upregulation of the RANK pathway and concomitant downregulation of the decoy receptor antagonist osteoprotegerin. Denosumab might help to restore homeostasis to both osteoclasts and osteoblasts and, therefore, might normalize serum calcium. This observation has been the basis for several ongoing clinical trials assessing denosumab therapy for patients with HCM.[11,12] At the University of North Carolina Medical Center, 4 patients with multiple myeloma and renal dysfunction who were deemed ineligible for bisphosphonate therapy have received denosumab for the treatment of HCM. The present case report summarizes our current experience with the use of denosumab for the management of HCM in the setting of renal dysfunction.

Case Report

We have chronicled the following 4 cases of patients who presented with refractory HCM secondary to multiple myeloma in the setting of renal dysfunction. We have also included a novel dosing strategy for denosumab in patients with HCM to minimize the risk of long-term hypocalcemia associated with denosumab therapy. Their mean ± standard error of the mean (SEM) serum creatinine was 4.4 ± 0.7 mg/dL, and the mean serum calcium was 12.9 ± 0.4 mg/dL. The patients received denosumab a mean of 19.8 ± 1.9 days after their most recent bisphosphonate treatment. Other baseline patient-specific characteristics are summarized in Tables 1 and 2. In the first case (patient 1), a fixed dose of denosumab 60 mg was administered (0.79 mg/kg), which resulted in significant and prolonged hypocalcemia (calcium nadir, 6.9 mg/dL) requiring chronic intravenous calcium supplementation during a 5-month course (Table 3). To minimize the risk of hypocalcemia, the subsequent 3 patients (patients 2-4) received a weight-based regimen of 0.3 mg/kg in accordance with the results from a dose-escalation phase I study.[13] These patients achieved normalization of their serum calcium after a mean of 8.6 ± 2.9 days, with a mean nadir of 7.6 ± 1.9 mg/dL. Figure 1 illustrates corrected serum calcium values following denosumab administration for all 4 patients. Patient 4 appeared unresponsive to therapy and was transitioned to hospice care. Patient 1 was considered to have stable chronic kidney disease, and the patient's renal function did not significantly improve or worsen during hospitalization. All other patients were considered to have acute kidney injury. Patients 2 and 4 did not return to baseline renal function. In contrast, patient 3 returned to baseline renal function (serum creatinine, 0.9-1.2 mg/dL). Patient 2 required intermittent dialysis and patient 3 required intermittent dialysis and plasmapheresis for management of acute kidney injury associated with multiple myeloma. Patients 1, 3, and 4 had previous episodes of HCM. It is unknown whether patient 2 had experienced previous episodes, because most of her prior care for multiple myeloma had been at an outside institution.

Discussion

To our knowledge, only a single case report has been published of using denosumab in the setting of bisphosphonate-refractory HCM in 1 patient with metastatic renal cell carcinoma. However, the specific dosing was not outlined in the report.[14] Likewise, a case report has been published of a single 60-mg denosumab dose that caused persistent hypocalcemia in a patient with renal dysfunction being treated for osteoporosis.[16] A phase II trial is currently assessing denosumab use in patients with HCM and previous intravenous bisphosphonate therapy using a dose of denosumab of 120 mg every 4 weeks, with additional loading doses of 120 mg given on days 8 and 15 of treatment.[11,12] The primary endpoint is the proportion of subjects with a response, which the investigators defined as a corrected serum calcium level of ≤ 11.5 mg/dL within 10 days of the first denosumab dose.[11,12] The dosing regimen in the phase II study is strikingly different than the single doses of denosumab administered to patients with renal insufficiency in the present case report.

Additionally, 2 meta-analyses, available only in abstract form to date, have provided additional insight into the effect of denosumab in managing HCM. The first trial analyzed data from 3 phase III clinical trials and found that denosumab delayed the development of the first SRE or HCM compared with zoledronic acid (hazard ratio [HR], 0.83; 95% CI, 0.76-0.90; $P < .0001$).[15] The second trial analyzed data from 2 phase III clinical trials and found that denosumab delayed the development of first HCM compared with zoledronic acid (HR, 0.63; 95% CI, 041-0.98; $P = .04$) and delayed the development of first and subsequent HCM compared with zoledronic acid (relative risk, 0.48; 95% CI, 0.29-0.81; $P = .006$).[16] All patients in the denosumab arm of these studies received a dose of 120 mg every 4 weeks.[2,7]

In the present case report, 4 patients with renal dysfunction received dose-reduced denosumab therapy. Patient 1 had received a single fixed dose of denosumab 60 mg for HCM refractory to bisphosphonates. The patient experienced persistent hypocalcemia

Table 1 Baseline Clinical Characteristics

Pt. No.	Age (year)	Gender	Cytogenetics	Stage at Diagnosis	M Protein	Interval Since Diagnosis (year)	Previous Chemotherapy (n)	Interval Since Bone Marrow Transplantation (year)
1	64	Male	Complex	III	Nonsecretory	0.2	2	NA
2	75	Male	+Y	I	IgAκ	10.7	6	1.6
3	66	Female	Normal	I	IgGλ	5.7	4	4.0
4	55	Female	Del13q, p53 mutated	III	IgGκ	13.3	14	4.3

Abbreviations: Ig = immunoglobulin; M = monoclonal; NA = not available; Pt. No. = patient number.