

## CLINICAL VIGNETTE

# Denosumab for the Treatment of Bisphosphonate Refractory Hypercalcemia of Malignancy

Theresa L. Nilson, M.D., and Erik L. Lum, M.D.

### *Introduction*

Hypercalcemia is common in patients with malignancy, occurring in 20-30% of patients.<sup>1</sup> Volume expansion with normal saline is the mainstay of therapy with the addition of intravenous bisphosphonates in cases of severe hypercalcemia. Here we describe a case of bisphosphonate resistant hypercalcemia of malignancy and discuss potential treatment options for refractory cases.

### *Case Presentation*

A 62-year-old Caucasian male presented to the emergency department after being referred by his primary care physician with a stage 4 decubitus ulcer.

The patient had a long-standing history of decubitus ulcers following a fall from a balcony resulting in T2 paraplegia 24 years prior. He had no prior history of surgical reconstruction. This most recent ulcer began developing 6 weeks ago and was initially managed with wound care dressings. However, one week prior to presentation the patient noticed purulent drainage from his wound and was started on oral antibiotic therapy.

On initial presentation, he had a temperature of 36°C, blood pressure 104/55 mmHg, pulse of 79 beats per minute, and a respiratory rate of 13. In general, he was in no acute distress and appeared his stated age. His heart showed a regular rate and rhythm. There were no murmurs, gallops, or rubs appreciated. The lungs were clear to auscultation bilaterally. Examination of his back revealed a 10 by 10 cm stage IV decubitus ulcer with malodorous brownish-grey purulent discharge. The bone and ligaments of the spine were visible. Initial laboratory data showed a white blood cell count of 18.7, hemoglobin of 4.9 g/dL, hematocrit of 17.5%, and platelet count of 408. His basic metabolic panel had no abnormalities.

The initial evaluation of the patient's anemia revealed iron deficiency. He was transfused 3 units of packed red blood cells and started on empiric antibiotic therapy. Four days following admission, the patient underwent bone biopsy to rule out osteomyelitis, which revealed invasive squamous cell carcinoma. A CT scan of the abdomen and pelvis demonstrated metastatic disease with pelvic tumor infiltrates and diffuse inguinal lymphadenopathy. During this time, the patient's serum calcium increased from 8.8 mg/dL to 14.1 mg/dL. Hypercalcemia labs were sent, and the patient was

noted to have a low parathyroid hormone level of 12 pg/mL, low 1,25 vitamin D level of 6 pg/mL, and an elevated PTH-rP at 71 pg/mL. He was given a diagnosis of humoral hypercalcemia of malignancy and pamidronate 90 mg by intravenous infusion was administered. This reduced his calcium to 11 mg/dL over the course of 72 hours. However, his serum calcium increased to 13.4 mg/dL after 48 hours, and he was given another dose of pamidronate. The patient's serum calcium continued to rise to 15.3 mg/dL following the second infusion (Figure 1).

### *Discussion*

Hypercalcemia of malignancy is caused by one of three mechanisms: osteolytic metastases with local release of cytokines to cause bone resorption, ectopic PTH or PTH related protein, or synthesis of 1,25-dihydroxy vitamin D, which results in increased intestinal calcium absorption. In the presented case, the patient had an elevated PTH related peptide (PTHrP), low PTH, and low 1,25-dihydroxy vitamin D indicating excessive PTHrP as the cause of his hypercalcemia.

Parathyroid hormone related factors were first proposed to cause hypercalcemia in malignancy by Albright in the 1940s, based on clinical observations in patients with renal cell carcinoma.<sup>2</sup> It was not until 1987 when Moseley et al<sup>3</sup> were able to isolate PTHrP from a human lung cancer line that the causative protein was identified. PTHrP shares the same N terminal amino acid sequence as normal parathyroid hormone, and both react and interact with the type 1 PTH receptor to cause osteolysis and decrease calcium excretion by the kidney. Interestingly, PTHrP is less likely to stimulate renal production of 1,25 dihydroxyvitamin D.<sup>4</sup>

The treatment of hypercalcemia of malignancy depends on both the degree and acuity of onset. Patients with a serum calcium <14 mg/dL, and slow development may be able to tolerate hypercalcemia with minimal symptoms. These subsets of patients can be treated with isotonic saline to induce a urine output of 100 to 150 mL/hour. Volume expansion should reduce serum calcium by 1-2 mg/dL over 24-48 hours. Loop diuretics are no longer recommended routinely for patients with hypercalcemia.<sup>5</sup> Despite their known ability to increase renal calcium excretion, loop diuretics can worsen hypercalcemia by inducing volume depletion, and the high doses necessary to lower the serum calcium results in

clinically significant hypokalemia and hypomagnesemia. However, loop diuretics may be useful in patients who cannot tolerate aggressive volume expansion (i.e., those with heart failure or renal impairment).

For patients who have a serum calcium >14 mg/dL or develop rapid onset of hypercalcemia, additional therapy is warranted to reduce serum calcium. Intravenous administration of bisphosphonates has now become the mainstay of therapy in these cases. Bisphosphonates induce osteoclast apoptosis to reduce bone turnover and reduce calcium levels within 48-72 hours following administration.

In the case described above, the patient continued to have refractory hypercalcemia despite two doses of pamidronate. The treatment options for patients with bisphosphonate refractory hypercalcemia are limited to denosumab and hemodialysis. Denosumab is a human monoclonal antibody against RANK-Ligand (RANKL). RANKL binds to RANK on pre-osteoclasts to promote their maturation into osteoclasts. The largest case series published by Hu et al<sup>6</sup> 33 indicated that patients with hypercalcemia of malignancy refractory to traditional bisphosphonate therapy were given denosumab on days 1, 8 15, and 29 and then every 4 weeks lead to a reduction in hypercalcemia in 64% of patients within 10 days of therapy with a sustained effect over an average of 104 days.

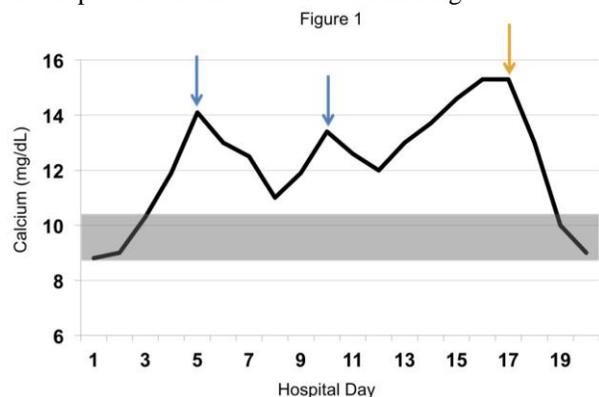
Hemodialysis with low or no calcium dialysis fluid is an effective mechanism of rapidly lowering serum calcium levels. HD should be reserved for patients with extreme elevations in serum calcium or in symptomatic patients where rapid correction is necessary. However, without additional therapy hypercalcemia will recur.

### Conclusion

The patient was given a single dose of dose denosumab, and his serum calcium decreased to 9.32mg/L over 96 hours. The response was sustained without additional need for infusion for 2 months before the patient expired from infectious complications related to his decubitus ulcer.

### Figures

**Figure 1:** Depiction of patient's serum calcium from admission. Blue arrows indicate infusion of pamidronate. The orange arrow indicates denosumab administration. Shaded area represents normal serum calcium range.



### REFERENCES

1. **Stewart AF.** Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* 2005 Jan 27;352(4):373-9. Review. PubMed PMID: 15673803.
2. **Albright F.** Case records of the Massachusetts General Hospital: Case 39061. *N Engl J Med.* 225:789-96. 1941
3. **Moseley JM, Kubota M, Diefenbach-Jagger H, Wettenthal RE, Kemp BE, Suva LJ, Rodda CP, Ebeling PR, Hudson PJ, Zajac JD, et al.** Parathyroid hormone-related protein purified from a human lung cancer cell line. *Proc Natl Acad Sci U S A.* 1987 Jul;84(14):5048-52. PubMed PMID: 2885845; PubMed Central PMCID: PMC305244.
4. **Guise TA, Mundy GR.** Cancer and bone. *Endocr Rev.* 1998 Feb;19(1):18-54. Review. PubMed PMID: 9494779.
5. **LeGrand SB, Leskuski D, Zama I.** Narrative review: furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med.* 2008 Aug 19;149(4):259-63. Review. PubMed PMID: 18711156.
6. **Hu MI, Glezerman IG, Leboulleux S, Insogna K, Gucalp R, Misiorowski W, Yu B, Zorsky P, Tosi D, Bessudo A, Jaccard A, Tonini G, Ying W, Braun A, Jain RK.** Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab.* 2014 Sep;99(9):3144-52. doi: 10.1210/jc.2014-1001. Epub 2014 Jun 10. PubMed PMID:24915117; PubMed Central PMCID: PMC4154084.

Submitted June 8, 2016