

Denosumab Use in a Patient with Bisphosphonate-Resistant Humoral Hypercalcemia of Malignancy

Maali Milhem, MD¹, M. Adeel Mahmood, MD¹, John W Leidy, MD-PhD²

Author affiliations:

1. Department of Internal Medicine, Marshall University Joan C. Edwards School of Medicine, Huntington, WV
2. Medical Service, VA Medical Center, Huntington, WV

All authors have no conflicts of interest to disclose.

Corresponding author:

Maali Milhem, MD
Endocrinology Fellow
Department of Internal Medicine
Joan C. Edwards School of Medicine
Marshall University
Huntington, West Virginia
Email: milhem@live.marshall.edu

Abstract

Objective: To describe the use of denosumab as an option for treating bisphosphonate-resistant humoral hypercalcemia of malignancy (HHM).

Methods: We present the clinical history and laboratory findings of a patient with a review of related literature.

Results: A 62 year-old male with stage IV laryngeal squamous cell carcinoma and lung metastases had multiple hospital admissions for asymptomatic hypercalcemia. The patient had no known bone metastases. His laboratory data showed a high calcium level, a low level of intact parathyroid hormone (PTH) and a high level of parathyroid hormone related peptide (PTHrP), which confirmed the diagnosis of humoral hypercalcemia of malignancy. There was atypically an elevated level of 1,25-dihydroxyvitamin D [1,25(OH)₂D]. The patient was treated with fluids, prednisone, calcitonin, and bisphosphonates. Hypercalcemia was refractory to bisphosphonate treatment as well as other modalities. Denosumab treatment was then added. Denosumab along with bisphosphonate produced an added effect on lowering calcium levels.

Conclusion: Denosumab provides potentially a new treatment option for bisphosphonate refractory humoral hypercalcemia of malignancy, especially in the presence of high PTHrP and 1,25(OH)₂D.

Key words: Hypercalcemia, squamous cell carcinoma, malignancy, denosumab, bisphosphonate, 1,25-dihydroxyvitamin D

Introduction:

Hypercalcemia has been reported to occur in 20-30% of cancer patients during the course of the disease. (1) Malignancy-associated hypercalcemia is the most common cause of hypercalcemia in hospitalized patients and is a predictor of a poor prognosis with an approximately 50% mortality rate within 30 days. (1) Although malignancy-associated hypercalcemia can be treated with intravenous bisphosphonates, patients may not respond or may relapse while receiving therapy. Denosumab is a fully human monoclonal antibody that binds to the mediator of bone resorption, receptor activator of nuclear factor kappa-B ligand (RANKL). (2) It was approved in 2010 for use in osteoporosis and metastatic bone disease. It has been used to treat refractory hypercalcemia of malignancy in case reports, (3-5) and single arm international studies have recently demonstrated effectiveness in treating bisphosphonate refractory hypercalcemia. (6,7)

Case Report:

A 62 year-old male patient with a significant smoking history was found to have multiple lung nodules on a pre-operative chest X-ray. Detailed workup showed laryngeal squamous cell cancer with metastases to lungs and mediastinal and hilar lymph nodes. He was treated with chemotherapy and radiotherapy.

The patient's calcium level was 11.3 mg/dl (normal: 8.5-10.3 mg/dl), and he was started on 4 mg intravenous zoledronic acid every 3 weeks for a total of 6 months. The patient was then admitted to the hospital with asymptomatic hypercalcemia with a calcium level of 13.3 mg/dl and an albumin-corrected calcium level of 13.8 mg/dl. He denied using hydrochlorothiazide, calcium, or vitamin D. Other measures used such as fluid hydration, pamidronate (90 mg), and calcitonin resulted in an improvement in the calcium level but it did not normalize (Figure 1). An evaluation for hypercalcemia showed normal phosphorus and creatinine levels. In addition, the patient had an intact PTH of 9 pg/ml (normal: 11-54 pg/ml), PTHrP of 16 pmol/L (normal < 1.8), 25(OH) vitamin D of 17ng/ml (normal: 30-100 ng/ml) and 1,25 (OH)₂D of 134 pg/ml (normal: 10-75 pg/ml). Thyroid stimulating hormone (TSH) was 19.8 IU/ml (normal: 0.35-5.50 IU/ml) and free thyroxine was 1 ng/dl (normal: 0.93-1.71 ng/dl). There was no clinical evidence of coexisting lymphoma or granulomatous disease to explain the elevated 1,25 (OH)₂D. These findings were consistent with HHM with an atypically elevated 1,25 (OH)₂D. Given the elevated 1,25(OH)₂D, prednisone 10 mg was added at the time of discharge to suppress 1- α -hydroxylase activity. Levothyroxine (50 mcg) was added to treat hypothyroidism.

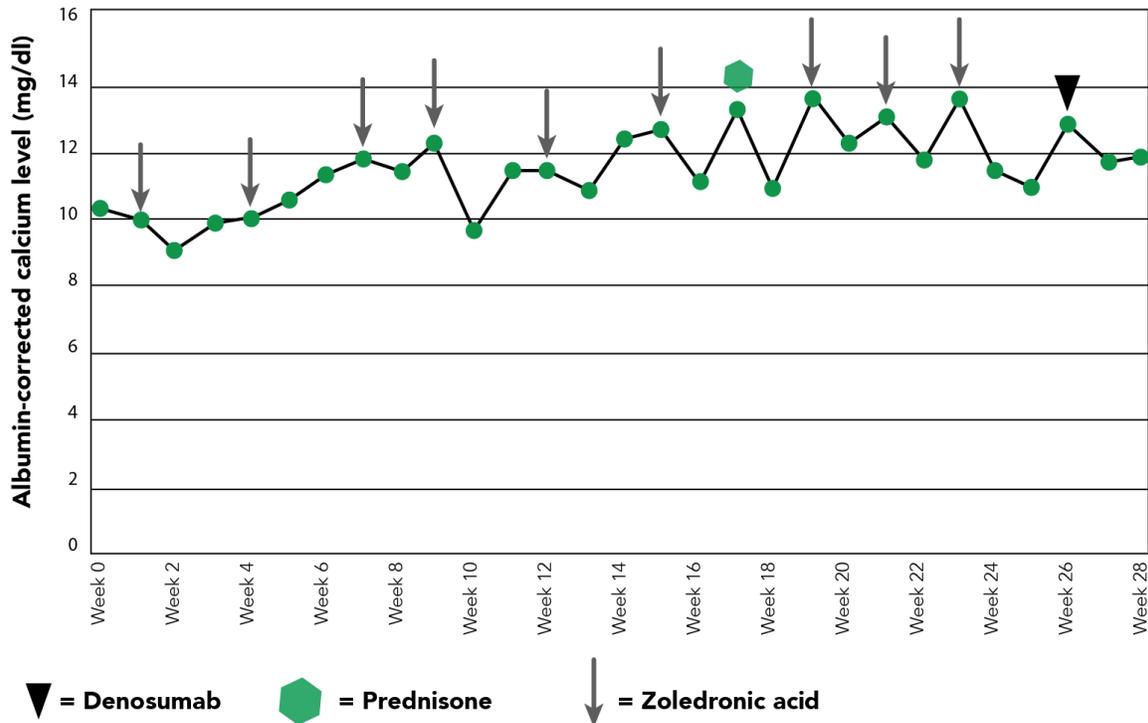


Figure 1: The response of the albumin-corrected calcium level of the patient to prednisone, zoledronic acid, and denosumab. His level responded initially to zoledronic acid infusion but it continued to recur with a progressively higher level. The last arrow shows the effect of denosumab on the albumin-corrected calcium level.

This patient's hypercalcemia became increasingly difficult to control. Despite an increase of zoledronic acid administration every 2 weeks and the addition of prednisone, he had four subsequent admissions with corrected-calcium as high as 14.2 mg/dl (Figure 1). At this time, denosumab 120 mg was administered subcutaneously, as an off-label use to treat bisphosphonate-refractory hypercalcemia. The albumin corrected-calcium level remained subsequently less than 12 mg/dl for two weeks (Figure 1). The patient unfortunately continued to experience rapid disease progression and finally decided for comfort care measures.

Discussion:

We present a patient with metastatic squamous cell carcinoma and hypercalcemia of malignancy with simultaneous elevations of PTHrP and 1,25(OH)₂D. He fulfilled the criteria for the diagnosis of HHM. After failing to respond to frequent administration of bisphosphonates and oral prednisone, hypercalcemia improved with the addition of denosumab.

HHM is a paraneoplastic manifestation frequently of squamous cell carcinoma with elevation of circulating PTHrP. The amino terminus of PTHrP binds to the type 1 PTH/PTHrP receptor, PTHR1, a member of the seven-transmembrane-spanning G-protein-coupled receptor family. (8)

Both PTH and PTHrP can produce hypercalcemia by increasing the resorption of bone throughout the skeleton and the renal reabsorption of calcium. (9,10) There are differences in the patterns of receptor activation between PTH and PTHrP due to differences in the C-terminal portions of the peptides. (8) PTH stimulates both bone resorption and formation, while PTHrP stimulates mainly bone resorption. (10) Despite the action of PTHrP through the common PTHR1 receptor, this pathway represents a poor stimulus for 1- α -hydroxylation compared to PTH, such that 1,25(OH)₂D is often low or normal in patients with HHM. (11) Clinical studies have shown a chronic infusion of PTHrP is a poor stimulator of 1,25(OH)₂D production. (12,13) The interactions between osteoclasts and cancer cells are mainly mediated by PTHrP, which stimulates osteoblasts to promote production of RANKL with the formation of osteoclast precursors and subsequent bone osteolysis. (14)

Serum levels of 1,25(OH)₂D are generally suppressed or normal in patients with HHM, (11,15) instead this patient showed an atypical high level of 1,25(OH)₂D, which may have contributed to the hypercalcemia.

Intravenous bisphosphonates are considered as first line treatment for HHM. However, hypercalcemia may not respond or may relapse while the patient is receiving bisphosphonate therapy. In clinical studies of patients treated with zoledronic acid or pamidronate, 26% relapsed and another 19% had an incomplete response to treatment. (16) The efficacy of bisphosphonates is influenced by several factors: 1) the mechanism of hypercalcemia (more effective in cases of hypercalcemia associated with bone metastases), 2) the level of hypercalcemia (higher doses are required to treat more severe hypercalcemia), and 3) higher levels of PTHrP (above 12 pmol/L) are associated with a lower response rate in humoral hypercalcemia (17,18). In addition, glucocorticoids have a role in the treatment of patients with hypercalcemia of malignancy who have elevated levels of 1,25(OH)₂D. (1,13)

Denosumab is a monoclonal antibody that binds to the bone resorption mediator RANKL preventing the ligand from binding to its receptor that in turn inhibits osteoclast development, activation, and survival. (2) Denosumab is FDA approved for preventing skeletal-related events in patients with solid malignancy, for preventing bone fractures in postmenopausal women with osteoporosis, and recently for treatment of hypercalcemia of malignancy. Hypocalcemia is one of the main adverse effects of this agent because of reduced osteoclast function, and this condition was significantly increased in patients treated with denosumab compared with zoledronic acid. (19)

Recent single-arm international studies evaluated denosumab for treatment of persistent hypercalcemia in patients with solid tumors or hematologic malignancies after incomplete response or relapse following bisphosphonates. (6, 7) Denosumab effectively lowered albumin-corrected calcium to ≤ 11.5 mg/dl in 64% of patients. (7) This study provided the results leading to FDA approval. Other considerations for using denosumab in hypercalcemia of malignancy are a creatinine clearance less than 30 or a history of bisphosphonate intolerance.

The patient in this case report, despite a high PTHrP greater than 12 pmol/L and an elevated 1,25(OH)₂D, showed some response to a single dose of denosumab, suggesting effectiveness of denosumab in the presence of high PTHrP and 1,25(OH)₂D and its different mechanism of

action may provide a possible reason for a response when there is a lack of response to bisphosphonates and glucocorticoids.

Conclusion:

Denosumab offers an option for the treatment of bisphosphonate refractory hypercalcemia of malignancy. This patient with HHM demonstrating highly elevated PTHrP and $1,25(\text{OH})_2\text{D}$ levels showed some response to a single dose of denosumab after relapse of response to bisphosphonates and glucocorticoids.

Acknowledgements

This material presented in part at the American Association of Clinical Endocrinologists, 23rd Annual Scientific and Clinical Congress, No. 633, 2014.

References:

1. Stewart AF. Hypercalcemia associated with cancer. *N Engl J Med.* 2005;352:373-379.
2. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone.* 2011; 48:677-692.
3. Khoury N, Chang J, Gru AA, et al. Resorptive hypercalcemia in post-essential thrombocythemia myelofibrosis: treatment with denosumab. *J Clin Endocrinol Metab.* 2012 Sep;97:3051-3015.
4. Vellanki P, Lange K, Elaraj D, et al. Denosumab for management of parathyroid carcinoma-mediated hypercalcemia. *J Clin Endocrinol Metab.* 2014;99:387-390.
5. Boikos SA, Hammers HJ. Denosumab for the treatment of bisphosphonate-refractory hypercalcemia. *J Clin Oncol.* 2012;30:e299. O
6. Hu MI, Glezerman I, Leboulleux S, et al. Denosumab for patients with persistent or relapsed hypercalcemia of malignancy despite recent bisphosphonate treatment. *J Natl Cancer Inst.* 2013;105: 1417–1420.
7. Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for Treatment of Hypercalcemia of Malignancy. *J Clin Endocrinol & Metab.* 2014;99 :3144-3152.
8. Wysolmerski JJ. Parathyroid hormone-related protein: an update. *J Clin Endocrinol Metab.* 2012; 97: 2947–2956.
9. Clines GA. Mechanisms and treatment of hypercalcemia of malignancy. *Curr Opin Endocrinol Diabetes Obes.* 2011;18:339–346.
10. Rosol TJ, Capen CC: Mechanism of cancer-induced hypercalcemia. *Lab Invest.* 1992; 67: 680-702 .
11. Schilling T, Pecherstorfer M, Blind E, et al. Parathyroid hormone-related protein (PTHrP) does not regulate 1,25-dihydroxyvitamin D serum levels in hypercalcemia of malignancy. *J Clin Endocrinol Metab.* 1993; 76: 801–803.
12. Horwitz MJ, Tedesco MB, Sereika SM, et al. Continuous infusion of parathyroid hormone versus parathyroid hormone-related protein in humans: discordant effects on 1,25(OH)₂ vitamin D and prolonged suppression of bone formation. *J Bone Min Res.* 2005;20:1792–1803.
13. Horwitz MJ, Stewart AF, Malignancy- associated hypercalcemia and medical management. Chapter 63. In: Jameson JL, De Groot LJ, eds. *Endocrinology: Adult and Pediatric.* 6th ed. Philadelphia, PA: Saunders Elsevier, 2010; 1198-1211.
14. Lumachi F, Brunello A, Roma A, et al. Cancer-induced hypercalcemia. *Anticancer Res.* 2009; 29: 1551-1556.
15. Stewart AF, Horst R, Deftos LJ, et al. Biochemical evaluation of patients with cancer-associated hypercalcemia: evidence for humoral and nonhumoral groups. *N Engl J Med.* 1980;303:1377–1383.
16. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol.* 2001;19:558–567.
17. Gurney H, Grill V, Martin TJ: Parathyroid hormone-related protein and response to pamidronate in tumor-induced hypercalcemia. *Lancet.* 1993; 341: 1611–1613.
18. Walls J, Ratcliffe WA, Howell A, et al. Response to intravenous bisphosphonate therapy in hypercalcaemic patients with and without bone metastases: the role of parathyroid hormone-related protein. *Br J Cancer.* 1994; 70: 169–172.
19. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer.* 2012;48:3082-3092.