Case Report

DENOSUMAB FOR THE TREATMENT OF REFRACTORY HYPERCALCEMIA IN METASTATIC PARATHYROID CARCINOMA

Saori Itoshima, MD[1]; Akiko Yuno, MD[1]; Tomomi Kato, MD[1]; Hidetoshi Kamada, MD[2]; Akemi Ikota, MD[1]; Takeshi Usui, MD, PhD[3]; Akira Shimatsu, MD, DMS[3]; Shigeki Koizumi, MD, PhD[1]

ABSTRACT

Objective: Parathyroid carcinoma is a rare malignant neoplasm. Hypercalcemia due to parathyroid carcinoma is often resistant to medical management in the advanced stage. Here we report the usefulness of denosumab as an option for managing refractory hypercalcemia in the setting of parathyroid carcinoma.

Methods: A 39-year-old Japanese female with metastatic parathyroid carcinoma was referred to our hospital due to frequent episodes of hypercalcemia. Upon admission, her respective serum calcium (Ca) and intact parathyroid hormone (PTH) levels were 13.3 mg/dL (reference range, 8.5-10.2 mg/dL) and 1,920 pg/mL (reference range, 10-65 pg/mL). Although her hypercalcemia initially responded to strengthened standard therapy, it became unmanageable as her disease progressed. A single denosumab injection dramatically decreased her hypercalcemia from 15.1 to 10.1 mg/dL within 10 days. Her Ca levels remained in the reference range for more than 1 month. Her hypercalcemia could be controlled by denosumab injected at a frequency lower than that used for the bone metastasis of malignant tumors.

Results: Although her serum PTH level increased to 4,130 pg/mL, her condition has remained good for the last 14 months.

Conclusions: Denosumab is a humanized monoclonal antibody that inhibits the receptor activator of nuclear factor-κB ligand (RANKL) and is a potentially important palliative treatment for refractory hypercalcemia due to parathyroid carcinoma. **(AACE Clinical Case Rep. 2015;2:e141-e144)**

Abbreviations:
Ca = calcium; **PTH** = parathyroid hormone; **RANK** = receptor activator of nuclear factor-κB; **RANKL** = receptor activator of nuclear factor-κB ligand; **TRACP-5b** = tartrate-resistant acid phosphatase 5b

INTRODUCTION

Parathyroid carcinoma is rarely encountered, but the resulting hypercalcemia is very difficult to manage in the advanced stage (1,2). The prognosis of parathyroid carcinoma is quite variable (3), and hypercalcemia and its complications might ultimately cause death. The definitive treatment for parathyroid carcinoma is surgery, but irradiation and medical therapy using cinacalcet, bisphosphonate, and fluid replacement with diuretics are also options (4). Although controlling hypercalcemia is of paramount importance, few therapies are effective in the majority of severe cases. Bisphosphonates decrease the skeletal efflux of calcium (Ca) bone by suppressing osteoclast-mediated bone resorption and overall bone turnover. Zoledronate is the most potent drug, although periodic monitoring of renal function is strongly recommended (5). Cinacalcet is a calcimimetic agent that reduces parathyroid hormone (PTH) secretion by binding to Ca-sensing receptors expressed on parathyroid cells (6). All of these agents have been used to control hypercalcemia in parathyroid carcinoma, but they are often poorly tolerated at the doses required for control.

Submitted for publication October 16, 2013
Accepted for publication November 27, 2013
From the [1]Department of Endocrinology and Metabolism and [2]Department of Breast Surgery, Kin-i-kyo Chuo Hospital, Sapporo, Japan; [3]Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan.
Address correspondence to Dr. Akiko Yuno; Department of Endocrinology and Metabolism, Kin-i-kyo Chuo Hospital; 9-1,5-2 Higashi-ku Higashi-naebo, Saporo, Hokkaido 007-8505, Japan.
E-mail: yuno@kin-ikyo-chuo.jp
Published as a Rapid Electronic Article in Press at http://www.journals.aace.com on January 21, 2014. DOI:10.4158/EP14449.CR
To purchase reprints of this article, please visit: www.aace.com/reprints.

Denosumab is a humanized monoclonal antibody that inhibits the receptor activator of nuclear factor-κB ligand (RANKL). It has been used to treat bone metastases in patients with advanced cancer or multiple myeloma (7-9) but is rarely used for PTH-induced hypercalcemia. The successful treatment of patients with metastatic parathyroid carcinoma with refractory hypercalcemia with denosumab was recently described in several reports (10-14). We provide an additional case of parathyroid carcinoma successfully treated with denosumab with injection intervals extended to as long as 3 months.

CASE REPORT

A Japanese female with metastatic parathyroid carcinoma was first referred to our hospital at age 37 because of frequent episodes of uncontrollable hypercalcemia. Her family history was unremarkable. She had undergone a left upper parathyroidectomy for primary hyperparathyroidism at the age of 34. Subsequent histologic analysis revealed the presence of parathyroid carcinoma, and a left hemithyroidectomy with bilateral radical neck dissection and irradiation were performed. Despite this, her serum PTH and Ca levels continued to gradually increase. At the age of 38, lung metastasis of the parathyroid carcinoma was demonstrated by histologic examination of a palliative lung tumor resection. Although her hypercalcemia was temporarily controlled after palliative surgery and standard therapy (i.e., cinacalcet at 75 mg/day and monthly administration of zoledronate at 4 mg), it became unmanageable with further disease progression.

Upon admission at age 39, her laboratory test results were consistent with primary hyperparathyroidism and showed elevated levels of serum Ca 13.3 mg/dL (reference range, 8.5-10.2 mg/dL) and PTH 1,920 pg/mL (reference range, 10-65 pg/mL). Tartrate-resistant acid phosphatase 5b (TRACP-5b) is an enzyme that is expressed in high amounts by bone-resorbing osteoclasts, and it is useful as a marker of osteoclastic bone resorption (15). The patient's level of TRACP-5b was >1,500 mU/dL (reference range, 125-420 mU/dL). Hybrid single-photon emission computed tomography/computed tomography using technetium 99mTc-sestamibi revealed a 2-cm mass in the hypopharynx. Computed tomography of the chest showed enlargement of residual metastatic lung tumors.

To control her hypercalcemia, we increased the frequency of intravenous zoledronate administration, and the dose of cinacalcet was increased to 200 mg daily. Her Ca levels temporarily decreased from 13.3 to 11.8 mg/dL but then gradually increased to 15.1 mg/dL, indicating refractoriness to conventional treatment. Due to the poor control of her hypercalcemia, denosumab (120 mg) was administered on day 21 of hospitalization based on its reported hypocalcemic effects. Her intractable hypercalcemia dramatically improved, with levels decreasing to 10.1 mg/dL within 10 days following the first denosumab dose and remaining between 8.5 and 12.6 mg/dL for 2 months. Cinacalcet was decreased to the original dose of 75 mg/day due to gastrointestinal side effects. Thereafter, she continued to receive denosumab (120 mg every 4 weeks) in addition to cinacalcet (75 mg/day) until her third dose. As her Ca levels remained in the reference range, the denosumab injection frequency was decreased to every 12 to 15 weeks (Fig. 1). While her PTH levels remained elevated, her TRACP-5b levels decreased to 147 mU/dL, indicating potent suppression of bone turnover. Her irritability decreased, and her condition has remained good. No additional treatments or admissions were required for 14 months. During the follow-up period, her hypopharynx and lung tumors enlarged, and her serum PTH level increased to 4,130 pg/mL; thus, the interval between denosumab injections was gradually decreased to 8 weeks (Fig. 1).

A recent study revealed a high frequency of genetic alterations in parathyroid carcinoma (16,17). As mutations in the cell division cycle 73 and multiple endocrine neoplasia 1 genes (*CDC73* and *MEN1*) can cause parathyroid carcinoma, genetic analyses were performed, but polymerase chain reaction-direct sequencing of all the coding exons revealed no abnormalities.

DISCUSSION

Although parathyroid carcinoma is a rare cause of refractory hypercalcemia, elevated serum Ca levels are a major cause of death in this group of patients (1-3). Individuals with parathyroid carcinoma typically present with symptoms of hypercalcemia, bone damage caused by PTH excess, and occasionally neck masses. The majority of parathyroid carcinomas are sporadic and initially difficult to differentiate from far more common benign parathyroid adenomas. In the absence of clinical guidelines, patients with primary hyperparathyroidism are often not systematically assessed for their risk of malignancy before local excision of the tumor (1). Local resection for parathyroid carcinoma is associated with a high risk of recurrence and death (3). Some reports suggest the benefits of cytotoxic reagents for parathyroid carcinoma, and external-beam radiotherapy might be a valuable adjunct to surgery. One of the main treatment goals in parathyroid carcinoma is controlling hyperparathyroidism by eradicating the source of PTH secretion. Palliative therapies (e.g., bisphosphonates and Ca receptor agonists) that target PTH excess, are often used in combination. In the present case, combined treatment with bisphosphonates and cinacalcet initially resulted in reasonable control of the hypercalcemia, but this approach eventually failed, even when high doses were administered.

Denosumab is a humanized monoclonal antibody that inhibits RANKL. Initially, denosumab was introduced to treat osteoporosis and skeletal-related events such as fractures (18). Hypocalcemia emerged as one of the main

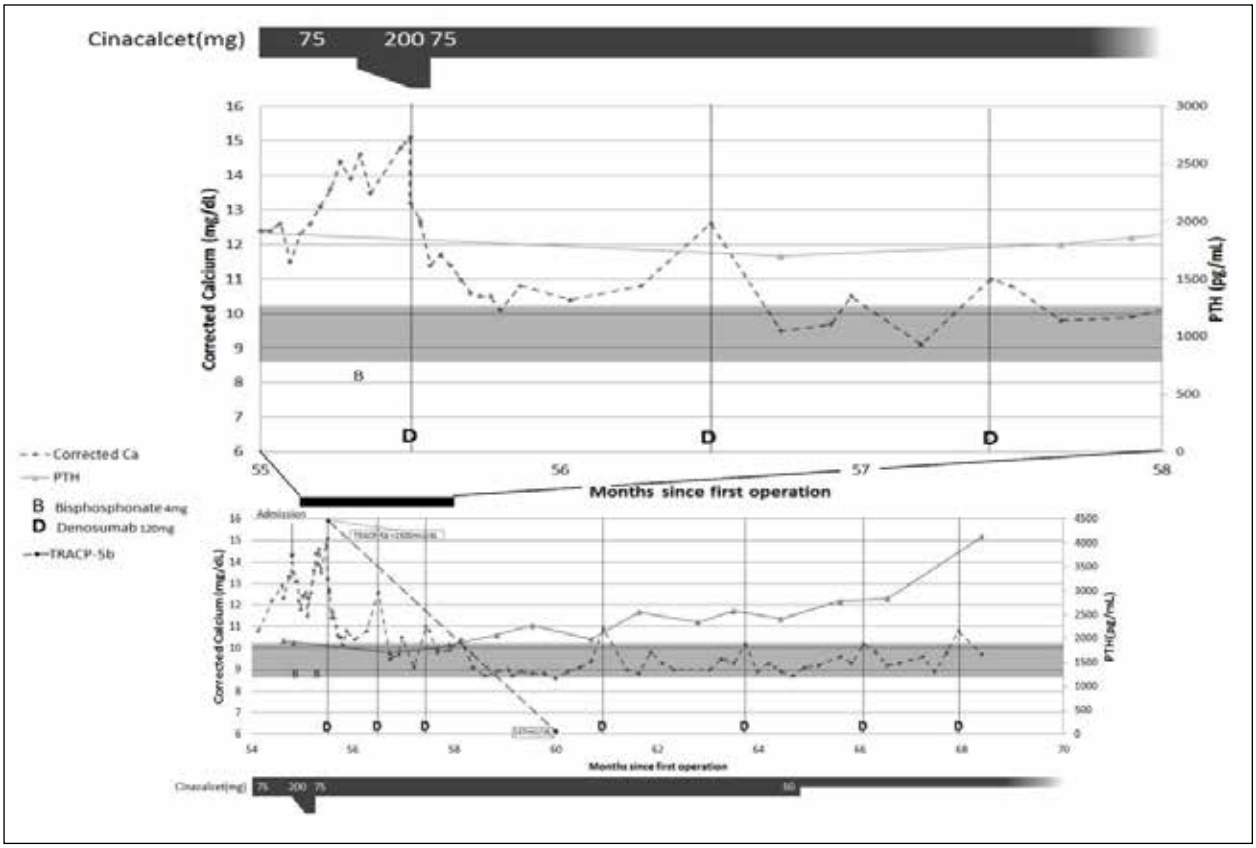

Fig. 1. Graphic illustration of the time courses of the levels of Ca (circles, dotted line, scale on the left axis), PTH (triangles, double line, scale on the right axis), and TRACP-5b (circles, double line). The administrations of denosumab (D) and intravenous bisphosphonates (B) are also indicated. *Ca* = calcium; *PTH* = parathyroid hormone; *TRACP-5b* = tartrate-resistant acid phosphatase 5b.

adverse effects of denosumab (9), which demonstrated potentially potent effects of denosumab in the setting of malignant hypercalcemia. The use of denosumab for managing hyperparathyroid-related hypercalcemia is rational because PTH indirectly triggers osteoclast bone resorption by stimulating osteoblasts to secrete RANKL, which binds to RANK expressed on osteoclasts.

The present case, together with recent reports, clearly demonstrates the efficacy of denosumab for refractory hypercalcemia due to parathyroid carcinoma (10-14). The initial treatment with denosumab in the present case was based on the standard protocol for bone metastases in patients with advanced cancer, in which loading doses of denosumab are 120 mg every 4 weeks (7-9). In recent reported cases of parathyroid carcinoma-mediated hypercalcemia, dosing intervals of denosumab were as short as 1 month (10-12). In the present patient, although PTH levels increased to 4,130 pg/mL, it is noteworthy that her hypercalcemia could be controlled by less frequent injection, up to 3 months without adverse events. Although parathyroid carcinoma is a slow-glowing tumor, poor control of hypercalcemia significantly reduces the quality of life as it results in various complications, multiple hospital admissions, and frequent doctor visits. Denosumab offered prolonged Ca control with less frequent administration and fewer hospital visits, thus improving patient quality of life.

CONCLUSION

In conclusion, less frequent injection of denosumab might be a useful treatment for refractory hypercalcemia associated with parathyroid carcinoma.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Schulte KM, Talat N.** Diagnosis and management of parathyroid cancer. *Nat Rev Endocrinol*. 2012;8:612-622.
2. **Wei CH, Harari A.** Parathyroid carcinoma: update and guidelines for management. *Curr Treat Options Oncol*. 2012;13:11-23.
3. **Talat N, Schulte KM.** Clinical presentation, staging and long-term evolution of parathyroid cancer. *Ann Surg Oncol*. 2010;17:2156-2174.
4. **Shane E.** Clinical review 122: Parathyroid carcinoma. *J Clin Endocrinol Metab*. 2001;86:485-493.

5. **Lumachi F, Basso SM, Basso U.** Parathyroid cancer: etiology, clinical presentation and treatment. *Anticancer Res*. 2006;26:4803-4807.
6. **Silverberg SJ, Rubin MR, Faiman C, et al.** Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. *J Clin Endocrinol Metab*. 2007;92:3803-3808.
7. **Stopeck AT, Lipton A, Body JJ, et al.** Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010;28:5132-5139.
8. **Henry DH, Costa L, Goldwasser F, et al.** Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011;29:1125-1132.
9. **Fizazi K, Carducci M, Smith M, et al.** Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377:813-822.
10. **Bowyer SE, White AM, Ransom DT, Davidson JA.** Resistant hypercalcaemia in metastatic parathyroid carcinoma. *Med J Aust*. 2013;198:559-561.
11. **Karuppiah D, Thanabalasingham G, Shine B, et al.** Refractory hypercalcaemia secondary to parathyroid carcinoma: response to high-dose denosumab. *Eur J Endocrinol*. 2014;171:K1-K5.
12. **Vellanki P, Lange K, Elaraj D, Kopp PA, El Muayed M.** Denosumab for management of parathyroid carcinoma-mediated hypercalcemia. *J Clin Endocrinol Metab*. 2014;99:387-390.
13. **Tong CV, Hussein Z, Noor NM, Mohamad M, Ng WF.** Use of denosumab in parathyroid carcinoma with refractory hypercalcemia. *QJM*. 2014;108:49-50.
14. **Nadarasa K, Theodoraki A, Kurzawinski TR, et al.** Denosumab for management of refractory hypercalcaemia in recurrent parathyroid carcinoma. *Eur J Endocrinol*. 2014;171:L7-L8.
15. **Halleen JM, Tiitinen SL, Ylipahkala H, Fagerlund KM, Väänänen HK.** Tartrate-resistant acid phosphatase 5b (TRACP 5b) as a marker of bone resorption. *Clin Lab*. 2006;52:499-509.
16. **Fernandez-Ranvier GG, Khanafshar E, Tacha D, et al.** Defining a molecular phenotype for benign and malignant parathyroid tumors. *Cancer*. 2009;115:334-344.
17. **Shattuck TM, Välimäki S, Obara T, et al.** Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. *N Engl J Med*. 2003;349:1722-1729.
18. **Cummings SR, San Martin J, McClung MR, et al.** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.