

[ CASE REPORT ]

## Prolonged Hypocalcemia Following a Single Dose of Denosumab for Diffuse Bone Metastasis of Gastric Cancer after Total Gastrectomy

Sakura Iizumi<sup>1</sup>, Tatsunori Shimoi<sup>1</sup>, Tadaaki Nishikawa<sup>1</sup>, Atsuko Kitano<sup>1</sup>, Shinsuke Sasada<sup>2</sup>, Akihiko Shimomura<sup>1</sup>, Emi Noguchi<sup>1</sup>, Mayu Yunokawa<sup>1</sup>, Kan Yonemori<sup>1</sup>, Chikako Shimizu<sup>1</sup>, Yasuhiro Fujiwara<sup>1</sup> and Kenji Tamura<sup>1</sup>

### Abstract:

Hypocalcemia is a significant adverse effect of denosumab. We herein report a case of prolonged hypocalcemia in a patient with multiple risk factors for hypocalcemia, including gastrectomy, increased bone turnover, and a poor performance status. Hypocalcemia developed after denosumab treatment for diffuse bone metastasis of gastric cancer, despite oral supplementation with vitamin D and calcium. To avoid serious prolonged hypocalcemia, a thorough assessment of the bone calcium metabolism is required before initiating denosumab treatment.

**Key words:** denosumab, hypocalcemia, gastrectomy, gastric cancer, vitamin D, bone turnover

(Intern Med 56: 2879-2882, 2017)

(DOI: 10.2169/internalmedicine.8908-17)

### Introduction

Bone metastasis leads to skeletal-related events (SREs), including pathologic fracture, the need for radiation or surgical treatment, and spinal cord compression, all of which impair a patient's quality of life. Clinical studies have shown that bone-modifying agents such as zoledronic acid and denosumab can reduce the incidence of SREs (1-3). Although denosumab has been associated with a lower frequency of SREs than zoledronic acid, it has also been associated with a higher frequency of hypocalcemia (4). We herein report a case of severe persistent hypocalcemia in a patient with diffuse bone metastasis of gastric cancer after the administration of a single dose of denosumab. Furthermore, we have identified potential risk factors for hypocalcemia, particularly gastrectomy, which has not been highlighted previously.

### Case Report

A 77-year-old woman was referred to our hospital to undergo treatment for malignant pleural effusions and dyspnea of 2 months' duration. She had undergone total gastrectomy with D2 lymphadenectomy and Roux-en-Y anastomosis for signet ring cell carcinoma of the stomach (pT1bN2M0, Stage IIA; Japanese Classification of Gastric Carcinoma, 14th Edition) (5) 12 years previously.

She was hospitalized to be evaluated and treated for dyspnea. Upon admission, her height and weight were 134.1 cm and 43.0 kg (body mass index: 23.9 kg/m<sup>2</sup>), respectively. Her Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 3. A laboratory evaluation yielded the following results: elevated levels of alkaline phosphatase (ALP; 5,680 IU/L, normal range: 115-359 IU/L) and carcinoembryonic antigen (CEA; 5.7 ng/mL, normal range: 0.0-5.0 ng/dL); normal levels of calcium (7.9 mg/dL), corrected calcium [serum calcium + (4 - serum albumin)]; 8.9 mg/dL,

<sup>1</sup>Department of Breast and Medical Oncology, National Cancer Center Hospital, Japan and <sup>2</sup>Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Japan

Received: January 20, 2017; Accepted: February 27, 2017; Advance Publication by J-STAGE: September 25, 2017

Correspondence to Dr. Tatsunori Shimoi, tshimoi@ncc.go.jp



**Figure 1. Bone scintigraphy. Diffusely increased activity can be seen in the skeleton. Little activity is observed in the kidneys.**

normal range: 8.8-10.1 mg/dL], and creatinine (0.51 mg/mL, normal range: 0.40-0.70 mg/dL). The estimated glomerular filtration rate (eGFR) and estimated creatinine clearance (Cockcroft-Gault equation) were 86 mL/min/1.73 m<sup>2</sup> and 62.7 mL/min, respectively. Her initial parathyroid hormone (PTH)-intact level was not measured.

Computed tomography revealed bilateral pleural effusion, ascites, and multiple sclerotic bone lesions without any other visceral metastases. No atrophic change of the kidneys was found. Bone scintigraphy revealed diffuse, increased skeletal activity with little renal activity, which met the definition of a super bone scan (Fig. 1) (6). A cytological evaluation of the pleural effusion detected adenocarcinoma, and a cell block specimen showed adenocarcinoma with signet-ring cells that were positive for Ber-EP4 and HNF4 $\alpha$  and negative for ER, PAX8, CDX2, and TTF-1, which was compatible with the patient's history of recurrent gastric cancer. She was diagnosed with pleural dissemination of recurrent gastric cancer and although ascites and bone lesions were not pathologically evaluated due to the challenges associated with specimen collection, these were respectively presumed to be malignant ascites and bone metastases of gastric cancer.

The patient elected to receive supportive care only, given her general condition and preference. To reduce the risk of SREs and maintain her activities of daily living, she received a single dose of denosumab (120 mg, subcutaneously), and the oral supplementation of calcium (610 mg/day), vitamin D (cholecalciferol) (400 IU/day), and magnesium (30 mg/day) was initiated. She was discharged the day after the administration of denosumab.

Six days after the administration of denosumab, she returned to our hospital via ambulance with paralysis and numbness in the hands. Blood tests revealed hypocalcemia (calcium, 4.7 mg/dL; corrected calcium, 6.0 mg/dL), and

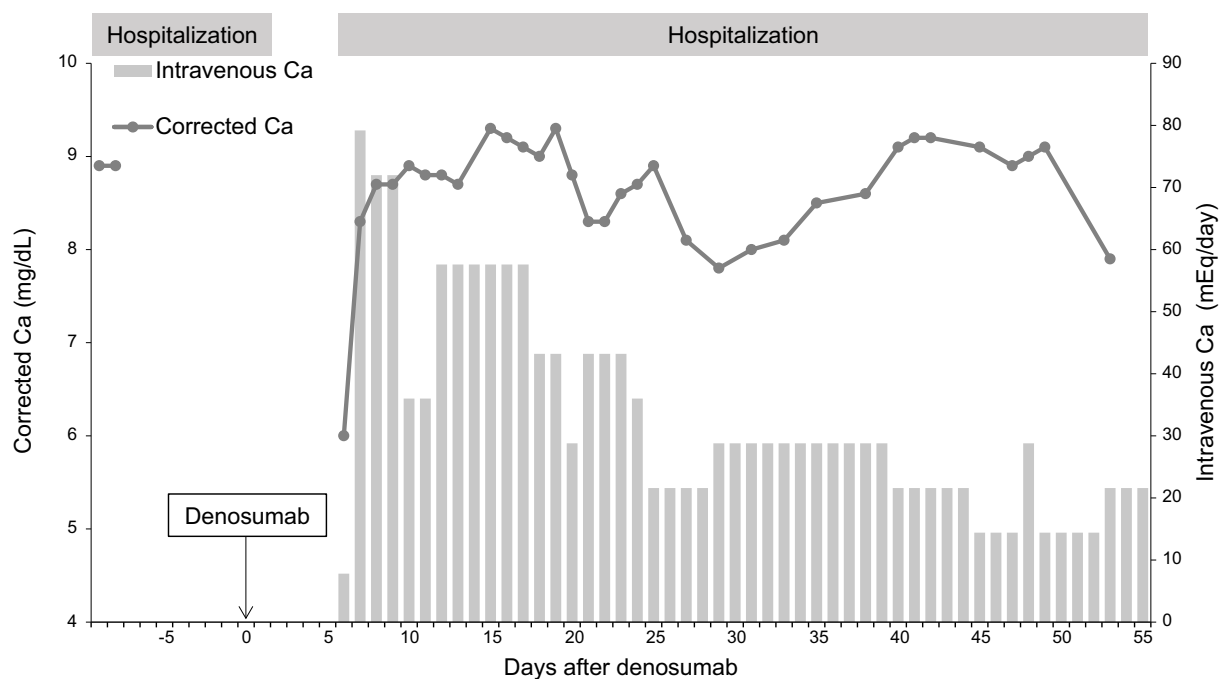
hypophosphatemia (phosphate, 2.3 mg/dL, normal range: 2.7-4.6 mg/dL), as well as the following additional values: magnesium, 2.8 mg/mL (normal range: 1.5-2.5 mg/dL); creatinine, 0.49 mg/mL; and ALP, 3605 IU/L. She received an infusion of 10 ml of 10% calcium gluconate (with 3.9 mEq calcium) followed by the continuous intravenous administration of calcium (2.5 mEq/h), after which her calcium level normalized. Twelve days after the administration of denosumab, the oral supplementation of calcium, vitamin D, and magnesium was restarted, and intravenous calcium was reduced to a dose equivalent to 18 mEq/day. Within a few hours, she experienced muscle weakness, and the intravenous calcium dosage was increased. Her PTH-intact level was found to be elevated to 375 pg/mL (normal range: 10-65 pg/mL). Fig. 2 shows the corrected calcium levels and the dose of calcium that was administered intravenously each day. Her general condition deteriorated gradually, with increasing pleural effusion and ascites. She required the intravenous administration of calcium until she was transferred to another hospital for palliative care 56 days later. She died 68 days after the administration of denosumab.

## Discussion

Denosumab, a monoclonal antibody that targets the receptor activator of nuclear factor- $\kappa$ B ligand (RANK-L), prevents bone resorption and bone destruction by inhibiting osteoclast activity (3). Three phase III trials demonstrated the superiority of this agent relative to zoledronic acid for the prevention and delay of SREs in patients with bone metastases of cancer (1-3). As mentioned above, hypocalcemia is a common side effect, which affects 5.5-13% of patients (1-3). Notably, a previous report suggested that RANK-L inhibitors are associated with a greater suppression of bone resorption and calcium release in comparison to bisphosphonates (7).

The factors associated with an increased risk of hypocalcemia include renal insufficiency, high bone turnover, and lack of vitamin D and calcium supplementation (8, 9). In our case, denosumab-induced hypocalcemia persisted for at least 7 weeks and necessitated the intravenous administration of calcium, despite the oral supplementation of calcium, vitamin D, magnesium, and phosphate. We hypothesize that the patient's history of total gastrectomy, increased bone turnover, and insufficient additional PTH secretion in response to decreased calcium were responsible for the duration and severity of hypocalcemia.

This report suggests that total gastrectomy with Roux-en-Y anastomosis, rather than gastric cancer, contributed to the development of hypocalcemia. Recently, a retrospective study of patients who received denosumab identified gastric cancer as an independent risk factor for hypocalcemia (10). Because gastrectomy did not increase the risk of hypocalcemia in that analysis, the researchers claimed that a gastrointestinal malfunction in patients with gastric cancer might be a mechanism underlying hypocalcemia, irrespective of gas-



**Figure 2.** Corrected Ca and intravenous Ca were administered each day. Ca: calcium

trectomy. However, fewer than 15 patients with gastric cancer were analyzed in that study, which was the number of cases in which denosumab was administered. Furthermore, the report did not consider the type of gastrectomy (total or partial gastrectomy) or reconstruction.

The mechanisms of calcium and vitamin D absorption suggest that hypocalcemia associated with total gastrectomy and Roux-en-Y anastomosis is more likely caused by malabsorption. For example, the use of Roux-en-Y anastomosis in bariatric surgery was associated with malabsorption of calcium and vitamin D (11). Another study reported suspected osteomalacia in 25% of post-gastrectomy patients and observed a correlation between fat malabsorption and abnormal calcium metabolism (12). Fat malabsorption is a known complication of gastrectomy with Roux-en-Y anastomosis (13) and can lead to impaired vitamin D absorption, as calcium is ionized and solubilized by gastric acid (14). After total gastrectomy, reduced gastric acid secretion would impair calcium ionization; furthermore, in patients with a Roux-en-Y anastomosis, chyme does not pass through the duodenum, where calcium is primarily absorbed (14). Extra caution should be taken when treating patients who have undergone gastrectomy because they may not absorb orally supplemented calcium or vitamin D. To the best of our knowledge, this is the first case report to demonstrate the possibility of an association between total gastrectomy and denosumab-related hypocalcemia.

Diffuse bone metastases, elevated ALP levels, and a poor PS are reported risk factors for hypocalcemia and may have led to denosumab-induced hypocalcemia in our patient. Although we did not measure the bone-specific ALP level, diffuse bone metastases and an elevated ALP level suggest a high bone metabolism. A pooled analysis of three phase III

studies of denosumab found that the number of bone metastases, an elevated bone-specific ALP level, and an elevated urinary N-telopeptide level, which are indicators of high bone turnover, are also risk factors for hypocalcemia (8). Furthermore, a poor PS was reported to be a risk factor for hypocalcemia (10). Altogether, this patient was probably at very high risk of developing denosumab-induced hypocalcemia.

Denosumab-induced hypocalcemia may persist in patients without an appropriate hormonal response to a decreased calcium level. In a phase II study that compared different denosumab doses and dosing schedules, a decrease in a urinary bone turnover marker persisted for 12 weeks after a single dose (15). Thus, bone resorption may be inhibited for at least 12 weeks. The persistence of hypocalcemia may depend on the patient's ability to compensate for this decreased calcium level. Previous case reports have described patients with prolonged denosumab-induced hypocalcemia who required intravenous calcium administration for more than 26 days (16-18). One of these reports identified the potential contributions of a gastrointestinal loss of calcium and normocalcemic hyperparathyroidism (18), with an inability to secrete additional PTH in response to a decreased calcium level. Although the baseline vitamin D, phosphate, and PTH levels were not measured in our case, it was hypothesized that the patient did not respond to decreased calcium levels and experienced persistent hypocalcemia requiring intravenous calcium administration for more than 50 days due to a gastrectomy-related loss of calcium and preexisting normocalcemic hyperparathyroidism.

The present study is associated with some limitations. First, it is possible that the PTH-intact level increased due to chronic renal dysfunction as the baseline PTH-intact level

was not measured and the assessment of the patient's kidney function was not thorough (24-hour urine collection was not performed). However, with the available data on the patient's renal function and the rarity (8%) of PTH-intact elevation ( $\geq 70$  pg/mL) in patients with an eGFR of  $\geq 60$  mL/min/1.73 m<sup>2</sup> (19), we believe that a marked increase in the PTH-intact level due to chronic renal dysfunction was unlikely. Second, in the present study, we only report one case. The association between gastrectomy and denosumab-induced hypocalcemia needs to be further evaluated in a larger number of patients with and without prior total gastrectomy. Nonetheless, it would be meaningful for clinicians to keep in mind the possibility that gastrectomy may increase the risk of denosumab-induced hypocalcemia and to identify potentially high-risk patients.

Total gastrectomy with Roux-en-Y anastomosis may be a risk factor for denosumab-induced hypocalcemia. This condition can persist in patients with impaired hormonal responses to decreased calcium levels. It is important to thoroughly evaluate bone and calcium homeostasis, including the nutritional status associated with gastrointestinal manipulation, and the extent of bone metastasis and turnover prior to the initiation of denosumab therapy.

**The authors state that they have no Conflict of Interest (COI).**

## References

1. 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* **28**: 5132-5139, 2010.
2. 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* **377**: 813-822, 2011.
3. 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* **29**: 1125-1132, 2011.
4. 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* **48**: 3082-3092, 2012.
5. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* **14**: 101-112, 2011.
6. Manier SM, Van Nostrand D. Super bone scan. *Semin Nucl Med* **14**: 46-47, 1984.
7. Morony S, Warmington K, Adamu S, et al. The inhibition of RANKL causes greater suppression of bone resorption and hypercalcemia compared with bisphosphonates in two models of humoral hypercalcemia of malignancy. *Endocrinology* **146**: 3235-3243, 2005.
8. Body JJ, Bone HG, de Boer RH, et al. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. *Eur J Cancer* **51**: 1812-1821, 2015.
9. Watkins KR, Rogers JE, Atkinson B. Tolerability of denosumab in metastatic solid tumor patients with renal insufficiency. *Support Care Cancer* **23**: 1657-1662, 2015.
10. Kinoshita Y, Arai M, Ito N, et al. High serum ALP level is associated with increased risk of denosumab-related hypocalcemia in patients with bone metastases from solid tumors. *Endocr J* **31**: 479-484, 2016.
11. Bland CM, Quidley AM, Love BL, Yeager C, McMichael B, Bookstaver PB. Long-term pharmacotherapy considerations in the bariatric surgery patient. *Am J Health Syst Pharm* **73**: 1230-1242, 2016.
12. Eddy RL. Metabolic bone disease after gastrectomy. *Am J Med* **50**: 442-449, 1971.
13. Stael von Holstein C, Walther B, Ibrahimbegovic E, Akesson B. Nutritional status after total and partial gastrectomy with Roux-en-Y reconstruction. *Bri J Surg* **78**: 1084-1087, 1991.
14. Bronner F, Pansu D. Nutritional aspects of calcium absorption. *J Nutr* **129**: 9-12, 1999.
15. Lipton A, Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* **25**: 4431-4437, 2007.
16. Shafqat H, Alquadan KF, Olszewski AJ. Severe hypocalcemia after denosumab in a patient with acquired Fanconi syndrome. *Osteoporos Int* **25**: 1187-1190, 2014.
17. Teng J, Abell S, Hicks RJ, et al. Protracted hypocalcaemia following a single dose of denosumab in humoral hypercalcaemia of malignancy due to PTHrP-secreting neuroendocrine tumour. *Clin Endocrinol* **81**: 940-942, 2014.
18. Milat F, Goh S, Gani LU, et al. Prolonged hypocalcemia following denosumab therapy in metastatic hormone refractory prostate cancer. *Bone* **55**: 305-308, 2013.
19. Muntner P, Jones TM, Hyre AD, et al. Association of serum intact parathyroid hormone with lower estimated glomerular filtration rate. *Clin J Am Soc Nephrol* **4**: 186-194, 2009.

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