

Prolonged zoledronic acid-induced hypocalcemia in hypercalcemia of malignancy

Shraddha Narechania, MD,^a Niroshan Thiruchelvam, MD,^a Chetan Lokhande, MD,^b Gaurav Kistangari, MD,^c and Hamed Daw, MD^d

^aDepartment of Internal Medicine, ^bOutcomes Research, ^cDepartment of Hospital Medicine, and ^dDepartment of Hematology and Oncology, Fairview Hospital, Cleveland, Ohio

Zoledronic acid is a parenteral long-acting bisphosphonate that has been shown to be more effective than other bisphosphonates in treating hypercalcemia of malignancy. It is important to be aware of its ability to induce prolonged and severe hypocalcemia (hypoCa) following administration, which can be difficult to control despite aggressive calcium replacement. We report on a patient with metastatic breast cancer who presented with severe symptomatic hypoCa after receiving zoledronic acid for hypercalcemia of malignancy.

Case presentation and summary

A 51-year-old woman was diagnosed with right-sided breast cancer in 2012 for which she underwent mastectomy and adjuvant chemoradiation. In 2013, she was found to have metastases to the axial skeleton, liver, and the left adrenal gland. She was scheduled to receive palliative chemotherapy with docetaxel, trastuzumab, and pertuzumab. Her medical history was significant for chronic renal insufficiency, gastroesophageal reflux disease, and nephrolithiasis. Her surgical history was significant for partial parathyroidectomy for primary hyperparathyroidism.

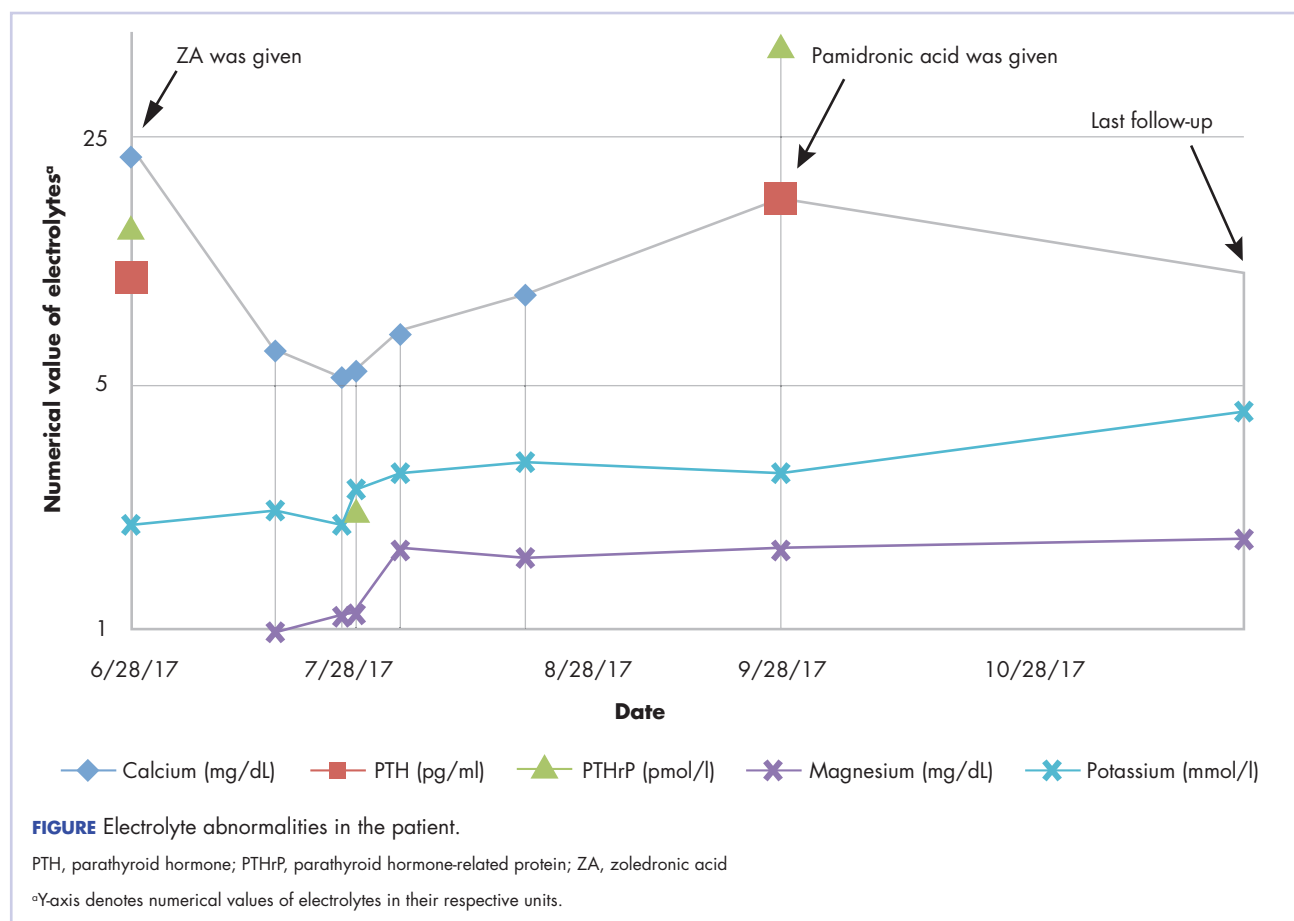
Before the patient could be started on any chemotherapy treatment for her metastatic cancer, she presented to the emergency department with polyuria, generalized weakness, and lethargy. Her physical examination was unremarkable. Laboratory tests were done, and she was found to have hypercalcemia of malignancy with a calcium level of 22 mg/dL (normal range, 8.5-10.5 mg/dL). Her other laboratory values included elevated parathyroid hormone-related protein (PTHrP) of 14 pmol/L (reference

value, <2 pmol/L), PTH of 10 pg/ml (normal range, 15-65 pg/ml), creatinine of 1.1 mg/dL, and creatinine clearance of approximately 65 ml/min (normal range, 88-128 ml/min). Testing for her vitamin D level was not done.

The patient received treatment with intravenous (IV) fluids, calcitonin, and a single 3.3-mg dose of IV zoledronic acid. After 6 days of treatment, her calcium levels decreased to 12.1 mg/dL, and she was discharged home. She received her first session of palliative chemotherapy a week after her discharge. Two weeks after the zoledronic acid treatment, the patient presented to the hospital with diarrhea as well as tingling and numbness all over the body. A physical examination of the patient was remarkable for carpopedal spasm of her upper extremities. The results of her lab tests were significant for a calcium level of 5.2 mg/dL, corrected level of 6.8 mg/dL, ionized calcium of 0.74 mmol/L, magnesium of 1.1 mg/dL (normal range, 1.7-2.6 mg/dL), and potassium of 2 mmol/L (normal range, 3.5-5 mmol/L). Her serum 25-hydroxy vitamin D level was 5.9 ng/ml (normal range, 8-15 ng/ml), consistent with severe vitamin D deficiency; her PTHrP was 2.2 pmol/L; and her PTH was 180 pg/ml, all of which was suggestive of secondary hyperparathyroidism owing to vitamin D deficiency and hypoCa. The results of an ECG showed sinus tachycardia and low voltage throughout but the corrected QT interval was normal.

The patient was started on a continuous IV calcium infusion after being given 2 grams of IV calcium and was monitored in the intensive care unit. She required 6-12 g of IV calcium daily in addition to high doses of oral calcium (up to 3.375 g) and repletion of potassium and magnesium during her

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hospital stay. She was discharged home on 5 g IV calcium, 100 mEq of potassium chloride, and 2 g magnesium daily, along with 50,000 units of vitamin D 3 times a week. She required that supplementation for 28 days after she was discharged, after which her calcium levels were replete. After 4 weeks off of calcium and vitamin D supplementation, she presented again with hypercalcemia of malignancy (Ca of 16.6 mg/dL) and with a PTHrP level of 44 pmol/L. She was given pamidronic acid 60 mg IV; this time she did not develop hypoCa because her vitamin D levels were replete.

Discussion

Several cases of severe hypoCa after bisphosphonate administration have been reported.¹⁻⁵ To our knowledge, this is the first case reported in literature showing severe deficiency of calcium, magnesium, and potassium requiring IV and oral supplements for a prolonged period after the administration of zoledronic acid for hypercalcemia of malignancy.

Hypercalcemia of malignancy is a potentially life-threatening complication seen most commonly in patients with breast cancer, lung cancer, and multiple myeloma, and it portends a poor prognosis.⁶ The mechanisms of hyper-

calcemia are multiple, the most common being humoral hypercalcemia of malignancy owing to the production of PTHrP by cancer cells. Other mechanisms include osteolytic metastases, which causes increased bone resorption by osteoclasts, and production of calcitriol by tumor cells.^{7,8} Management of hypercalcemia of malignancy includes aggressive hydration with IV fluids, combined with agents such as calcitonin. Bisphosphonates are often indicated for patients with symptomatic or severe (serum calcium, >14 mg/dL) hypercalcemia. The results from 2 large, double-blind, randomized, controlled trials demonstrated that zoledronic acid was superior to pamidronate in terms of efficacy and safety for the treatment of hypercalcemia of malignancy,⁹ which later led to its approval by the US Food and Drug administration for treatment of hypercalcemia of malignancy. The common adverse effects associated with the use of zoledronic acid include flu-like symptoms, including fever, myalgia, arthralgia and malaise, gastrointestinal effects, and renal insufficiency.

Bisphosphonates have a similar structure to that of pyrophosphate and attach to hydroxyapatite sites on the bone and inhibit osteoclast-mediated bone resorption in a variety of ways.¹⁰ Bisphosphonates have multiple uses

in clinical practice, including the treatment of osteoporosis, multiple myeloma, bone metastases, and hypercalcemia of malignancy. Intravenous bisphosphonates have 100% bioavailability, have a faster onset of action, and have the advantage of lesser gastrointestinal side effects unlike oral bisphosphonates such as alendronate. Zoledronic acid is one of the most potent bisphosphonates (it is at least a hundred times more potent in inhibiting bone resorption in preclinical studies) when compared with pamidronate acid.^{1,11} It is administered as an IV infusion over a short time of 5-15 minutes, which makes it preferable to other IV bisphosphonates.

However, bisphosphonates also affect mobilization of calcium and cause hypoCa. This side effect is exacerbated in patients who are clinically predisposed to hypoCa because of other factors such as vitamin D deficiency, hypomagnesemia, hypoparathyroidism, or renal insufficiency.¹²⁻¹⁴ It is also exacerbated in patients with osteoblastic bony metastases because of increased calcium uptake by osteoblasts.¹⁵ The body's normal response to counteract hypoCa is to increase secretion of PTH, which in turn increases the renal absorption of calcium, increases production of vitamin D to increase intestinal reabsorption of calcium, and increases serum calcium levels. This response is blunted in patients with pre-existing vitamin D deficiency as in the current case, and these patients are prone to hypoCa.¹⁶

In patients with renal insufficiency, tubular dysfunction leads to impaired reabsorption of calcium, and because bisphosphonates are renally excreted, this may impair their clearance from the body. Potent bisphosphonates such as zoledronate, pamidronate, and ibandronate are more likely to have a prolonged duration of action and can cause severe symptomatic hypoCa. Bergner et al showed that ibandronate has a lower toxicity profile compared with zoledronic acid or pamidronate when it is used in the setting of renal failure.¹⁷ However, pamidronate is the only bisphosphonate that can be administered in patients with a creatinine clearance of less than 30 ml/min, although data in this regard are limited. In the current case, the 3.3 mg of zoledronic acid that was given was appropriate for the degree of renal insufficiency the patient had.¹⁸ Our patient was at risk of getting hypocalcemic owing to a combination of the aforementioned factors, including hypomagnesemia, renal insufficiency, osteoblastic bony metastases, and vitamin D deficiency. Vitamin D supplementation is simple, easy, and inexpensive, so its measurement should be emphasized in clinical practice before the use of bisphosphonates.

Another important factor in the metabolism of calcium homeostasis is magnesium. Hypomagnesemia causes impaired synthesis of PTH and induces resistance of the bone and renal tubules to the effects of PTH, which is the major contributor to hypoCa.¹⁹ The causes of hypomagnesemia in the patient included prolonged diarrhea

and malnutrition. Of note, a retrospective study of 120 patients who had received zoledronic acid infusions demonstrated symptomatic hypocalcemia in 8% of the patients despite their having received appropriate dosing and supplementation of vitamin D and calcium before infusion.²⁰ Hypomagnesemia was found in all patients with hypoCa in that study.

Kreutle et al recommend checking calcium, phosphate, sodium, potassium, phosphate, and magnesium a week after bisphosphonate use, at least for the first time, and followed by subsequent checks every few months.² The side effects of bisphosphonates are frequently underestimated in clinical practice but they can have a significant effect on patient quality of life. For example, patients may require IV replacement of electrolytes at home for a long time, which will affect quality of life. There have also been reports of seizures occurring in patients who are on bisphosphonates owing to electrolyte disturbances.^{21,22} For that reason, it is important to be aware of the side effects and to take the necessary measures to prevent them. This will help in preventing unnecessary hospitalizations and reducing costs of care.

Conclusions

This report highlights the serious adverse effect of prolonged and sometimes life-threatening hypocalcemia as a result of bisphosphonate therapy in hypercalcemia of malignancy. In the current case, the administration of zoledronic acid in the setting of vitamin D deficiency and renal failure, led to severe, life-threatening hypocalcemia because of the impaired absorption of calcium and decreased clearance of zoledronic acid. Physicians who manage hypercalcemia of malignancy should be aware of the severe side-effect profile of zoledronic acid and screen all patients biochemically, including for vitamin D, magnesium, creatinine, and parathyroid hormone levels, before initiating therapy. We also recommend using a lower-potency bisphosphonate such as pamidronate, especially in patients who have previously developed severe hypocalcemia with zoledronic acid.

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