

## Cisplatin as an active treatment in zoledronate-refractory hypercalcemia

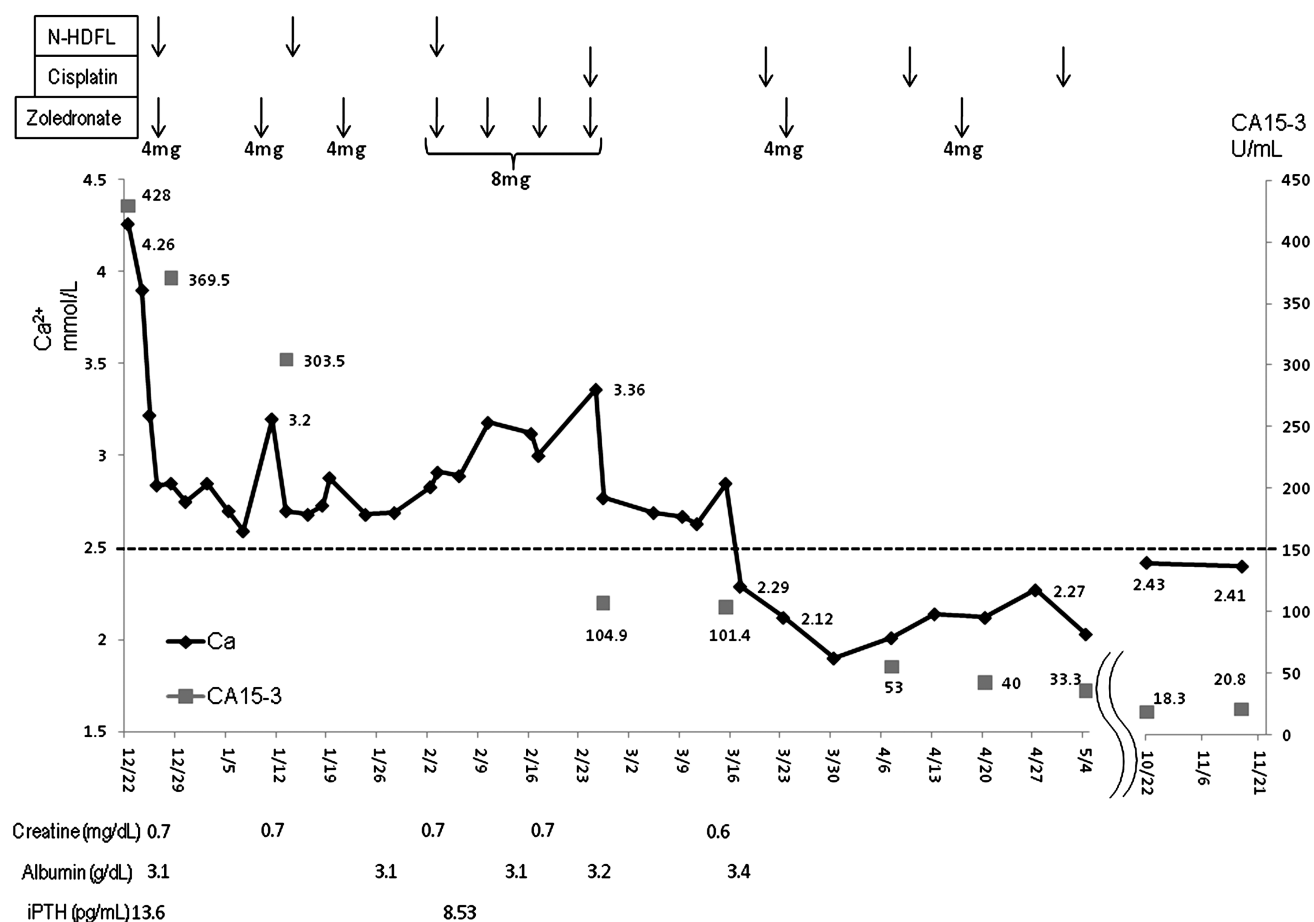
Hypercalcemia is one of the important oncologic emergencies in advanced malignancies [1]. After new-generation bisphosphonates (e.g. pamidronate and zoledronate) were discovered, the treatment of hypercalcemia in cancer patients has a great improvement [1]. Most patients with hypercalcemia are well controlled by bisphosphonates. However, we here report the first case of zoledronate-refractory hypercalcemia, successfully treated with cisplatin.

### case

A 58-year-old breast cancer patient who underwent left modified radical mastectomy in 1998 is reported here. The pathology showed infiltrating ductal carcinoma with positive expression of estrogen receptor and progesterone receptor. Recurrent breast cancer developed in 2008 October, and it was treated with exemestane. However, hormone therapy seemed ineffective. Laboratory examination revealed serum calcium of 4.26 mmol/l (normal 2.0–2.5 mmol/l); creatinine, 0.7 mg/dl (normal 0.6–1.3 mg/dl); estimated creatinine clearance rate, 86.2 ml/min; albumin, 3.1 g/dl (normal 3.5–5.0 g/dl); intact parathyroid hormone 13.6 pg/ml (normal 37–72 pg/ml); hemoglobin, 6.5 g/dl (normal 12–15 g/dl); platelet,  $34 \times 10^3/\mu\text{l}$  (normal  $13\text{--}39 \times 10^3/\mu\text{l}$ ); and D-dimer of 7.98  $\mu\text{g/ml}$  (normal  $<1 \mu\text{g/ml}$ ). The computer tomography scan showed multiple intraosseous metastatic tumors. She was admitted for disease progression and cancer-associated hypercalcemia and disseminated intravascular coagulation (DIC).

She received saline hydration, calcitonin, zoledronate and then chemotherapy with vinorelbine plus 24-h infusion of high-dose 5-fluorouracil and leucovorin (N-HDFL) (vinorelbine 25 mg/m<sup>2</sup> on days 1 and 8; high-dose 5-fluorouracil 2000 mg/m<sup>2</sup> and leucovorin 200 mg/m<sup>2</sup> on days 1 and 8, every 21 days per cycle) [2]. N-HDFL showed good efficacy to control the breast cancer. The CA 15-3 level decreased from 428 U/ml to 104.9 U/ml (Figure 1), DIC resolved with the hemogram returned to normal range, as well as with the decrease in size of those intraosseous mass.

However, the hypercalcemia persisted, not alone with the significant improvement of other cancer-associated parameters. We then increased the frequency of zoledronate administration from monthly to weekly, and doubled the dose from 4 to 8 mg; however, this aggressive treatment did not resolve hypercalcemia. We changed chemotherapy regimen from N-HDFL to single-agent cisplatin (35 mg/m<sup>2</sup> on days 1 and 8); dramatically, the calcium level was decreased to the normal



**Figure 1.** Serum calcium and CA 15-3 level through the treatment courses. N-HDFL, high-dose 5-fluorouracil and leucovorin; Ca, calcium.

range without further elevation afterward. CA 15-3 level was not changed (from 104.9 U/ml to 101.4 U/ml) after two cycles of cisplatin treatment but it slowly declined thereafter. The patient totally received seven cycles of cisplatin chemotherapy, and she is alive currently.

Hypercalcemia occurs in 20%–30% of cancer patients during their disease course and is one of the life-threatening oncologic emergencies, presented as lethargy, unconsciousness, cardiac arrhythmias, nausea, vomiting and polyuria. The mechanism of hypercalcemia is caused by direct bone metastases or parathyroid hormone-related proteins secreted from tumor cells. No matter what kind of pathogenesis of hypercalcemia, symptomatic hypercalcemia should be treated with antihypercalcemic therapies immediately, as well as the antitumor therapy to control the original cause. Zoledronate is one of the new generation of nitrogen-containing bisphosphonate that has high potency and longer effectiveness to block osteoclastic bone absorption so as to clinically be an effective antihypercalcemic therapy. Prior studies also described that zoledronate could overcome other bisphosphonate-resistant hypercalcemia, such as pamidronate-refractory hypercalcemia [3]. However, hypercalcemia of our patient was indeed refractory despite intensive treatment of zoledronate and tumor was well controlled by N-HDFL at that time. To our knowledge,

this case is the first report of zoledronate-refractory hypercalcemia.

Cisplatin is generally recognized as an old chemotherapy agent, but it had been reported that cisplatin could directly inhibit osteoclasts and reduce malignancy-associated hypercalcemia [4, 5]. However, clinical application of antihypercalcemic effect of cisplatin is not used currently because potent bisphosphonates are now widely available. In our patient, because hypercalcemia persisted under the condition of aggressive zoledronate treatment and effective chemotherapy, we tried to use cisplatin as a salvage antihypercalcemic therapy. Her serum calcium level dramatically decreased to the normal range. Although we could not exclude the possibility of partial antitumor effect by cisplatin, the rapid complete response to hypercalcemia reflected the fact that cisplatin played an important role in the antihypercalcemic treatment.

We clearly represent the first case of zoledronate-refractory hypercalcemia and demonstrate a significant antihypercalcemia activity of cisplatin in this patient. This observation indicates that cisplatin could be considered as an active treatment in malignancy-associated hypercalcemia following failure of bisphosphonate treatment and requires further studies.

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## disclosure

The author declare no conflict of interest.

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