

Oncology

Severe Hypophosphatemia Following Denosumab Administration in a Hemodialysis Patient with Progressive Prostate Cancer



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ABSTRACT

In a 68-year-old man on maintenance hemodialysis (HD), severe anemia was detected. Bone marrow biopsy was performed for investigation of pancytopenia and pathological examination revealed adenocarcinoma of the prostate. Prostate specific antigen (PSA) was 574 ng/mL. After androgen deprivation therapy was initiated, PSA decreased to 13.7 ng/mL. But subsequent elevation of PSA and pain due to bone metastases were recognized. Denosumab (120 mg) was administered. Although improvement of bone pain was observed, severe hypocalcemia occurred. Severe hypophosphatemia was subsequently detected. When we use denosumab in dialysis patients with advanced cancer, we should be careful of hypophosphatemia.

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Introduction

Bone metastasis is a frequent problem in patients with prostate cancer, breast cancer, and lung cancer, and about 75% of patients with metastatic cancer have bone metastases. These metastases are characterized by activation of osteoclasts and can cause severe skeletal-related events (SRE), which are defined as pathological fracture, radiation therapy or surgery for bone metastases, or spinal cord compression.¹ Therefore, it is important to reduce the occurrence of SRE.

Prostate cancer is particularly prone to metastasize to the bone. Due to the relatively long survival of prostate cancer patients after bone metastasis occurs, severe pain, pathological fractures, paralysis due to spinal cord compression, and hypercalcemia may develop and can significantly reduce QOL.

Denosumab is a human monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand (RANKL) that is believed to suppress SRE. Denosumab is a molecular targeting drug that specifically inhibits the binding of RANKL to RANK expressed on the cell membrane by osteoclasts and their precursor cells. Denosumab can be administered by subcutaneous injection, and dose reduction is not necessary even if the patient has renal dysfunction. In addition, occurrence of hypophosphatemia has been reported in less than 1% of patients receiving denosumab.

We managed a hemodialysis patient with progressive prostate cancer who developed severe hypophosphatemia following treatment with denosumab, and we report the clinical course here.

Case presentation

A 68-year-old man on maintenance hemodialysis (HD) was found to have severe anemia (Hb 6.1 g/dL) at a routine examination. Because pancytopenia (WBC 4000/ μ L, Hb 6.5 g/dL, platelets 76,000/ μ L) was identified, bone marrow biopsy was performed, and pathological examination revealed adenocarcinoma of the prostate. The prostate specific antigen (PSA) level was 574 ng/mL, strongly suggesting that he had prostate cancer. PSA had never been investigated previously in this patient. A hard nodule in the prostate gland was not detected by digital rectal examination, but prostate biopsy could not be done due to the low platelet count. Bone scintigraphy demonstrated systemic bone metastases (Fig. 1), but pelvic MRI did not reveal any obvious evidence of prostate cancer. CT scanning did not show lymph node metastases, we clinically diagnosed the tumor as T1N0M1b.

Androgen deprivation therapy (ADT) for prostate cancer with multiple bone metastases was commenced on April 20, 2012. PSA decreased from 574 ng/mL to 13.7 ng/mL after initiation of ADT. However, elevation of PSA occurred again subsequently along with pain from bone metastases, so denosumab (120 mg) was administered on October 23, 2012. Prior to injection of denosumab, the corrected calcium and phosphate levels were normal. Corrected

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Figure 1. Bone scintigraphy findings. Bone scintigraphy reveals multiple bone metastases before androgen deprivation therapy.

calcium decreased after denosumab was administered. The serum calcium concentration was maintained by monitoring corrected calcium frequently, increasing calcium supplementation, and addition of vitamin D (Fig. 2). Then the serum phosphate level became very low and phosphate did not increase much even after administration of phosphate binders was stopped.

For pain control, we administered an opioid at 60 mg daily. However, the opioid dose could be decreased to 40 mg daily after treatment with denosumab, which suggested that denosumab was effective for pain control. After the elevation of PSA was detected, he was continuously treated with flutamide (375 mg/day), dexamethasone sodium phosphate (1 mg/day), and ethinylestradiol (1 mg/day). However, the PSA level continued to increase. Appropriate blood transfusion was performed to control anemia.

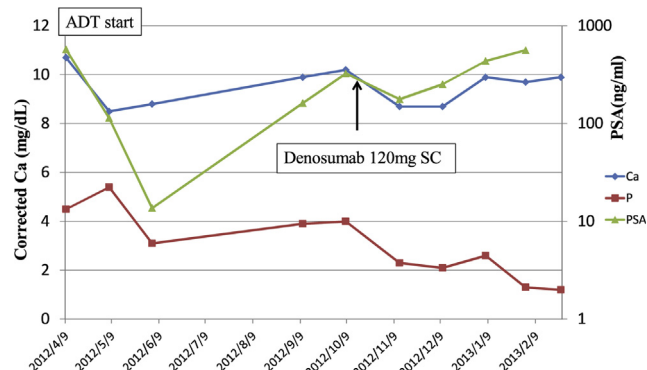


Figure 2. Change in corrected calcium (Ca), phosphate and PSA levels after denosumab treatment for prostate cancer. ADT, androgen deprivation therapy; PSA, prostate specific antigen; SC, subcutaneous.

Although he continued outpatient hemodialysis, loss of appetite occurred and it became difficult to live at home. The patient's general condition gradually worsened and he died in March 2013.

Discussion

There have been few reports about administration of denosumab to HD patients. In our patient with progressive prostate cancer, the effectiveness of denosumab for pain control was recognized since reduction of the opioid dose was possible after administration of denosumab. Although the corrected serum calcium level was maintained after denosumab administration, hypophosphatemia could not be corrected.

Denosumab is administered by subcutaneous injection. It is not necessary to perform dose adjustment in patients with renal dysfunction because a pharmacokinetic study did not show any differences of the concentration-time profile in relation to kidney function.² It has been suggested that patients with chronic kidney disease (CKD) are more dependent on parathyroid hormone (PTH)-mediated bone turnover and that inhibition of osteoclast activity leads to a "hungry bone-like syndrome",^{3,4} which means that the risk of hypocalcemia is high in CKD patients. In fact, it was reported that severe hypocalcemia occurs in 25% of patients with a PTH concentration of 300 or more.² Accordingly, it is necessary to administer denosumab with caution in patients who have high PTH levels.

A phase 3 study of denosumab treatment for men with castration-resistant prostate cancer indicated that hypocalcemia was manageable by appropriate supplementation with a combination of oral calcium and vitamin D.⁵

In hemodialysis patients, reabsorption of calcium from the urine and absorption from the gastrointestinal tract are reduced, so there is a possibility that the incidence of hypocalcemia could be increased. Therefore, adequate monitoring of the serum calcium concentration is needed in hemodialysis patients and administration of denosumab should be performed carefully until its efficacy and safety are clarified in randomized trials, because the usefulness of this agent for patients with stage 5 CKD has not been proven.

In the present patient, continuation of administration without decreasing the dose of denosumab was possible. Therefore, if denosumab is administered to patients with severe renal dysfunction such as hemodialysis patients, it seems possible to safely continue treatment while frequently monitoring the serum calcium concentration. As for the cause of hypophosphatemia during denosumab treatment, it was suspected to be related to tumor progression in our patient with multiple bone metastases and pancytopenia. Although we stopped treatment with phosphate binders, hypophosphatemia did not improve. Accordingly, it was considered to be related to progression of the underlying disease rather than to secondary hyperparathyroidism.

Conclusion

When denosumab is administered to hemodialysis patients with metastatic prostate cancer, it not only seems to be necessary to be careful about hypocalcemia but also hypophosphatemia.

Conflict of interest

There is no conflict of interest.

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