EJMI

DOI: 10.14744/ejmi.2021.48218
EJMI 2021;5(3):313–316

Research Article

Should Vitamin D Level be Measured Before Denosumab in Patients with Castration-Resistant Metastatic Prostate Cancer to Prevent Hypocalcemia?

Atike Gokcen Demiray, Arzu Yaren, Burcu Yapar Taskoylu, Serkan Degirmencioglu, Gamze Gokoz Dogu, Umut Cakiroglu, Nail Ozhan, Canan Karan, Burcin Cakan Demirel, Tolga Dogan, Melek Ozdemir

Department of Medical Oncology, Pamukkale University Faculty of Medicine, Denizli, Turkey

Abstract

Objectives: Denosumab reduces skeletal related events in castration-resistant metastatic prostate cancer (CRMPC) with bone metastases.It is recommended to give calcium and vitamin D to prevent hypocalcemia after denosumab. There is no recommendation to check vitamin D and the specific level of vitamin D that should not be given before denosumab. We aimed to show that the rate of hypocalcemia is high even in vitamin D deficiency alone in the absence of other risk factors for hypocalcemia and can be reduced by checking vitamin D before the administration or by adjusting the dose of denosumab according to the vitamin D, which are not included in denosumab product information (PI).

Methods: We retrospectively analyzed 40 CRMPC patients who received subcutaneous injections of 120 mg denosumab.

Results: 28 patients had vitamin D deficiency before treatment. Patients with vitamin D deficiency had a higher rate of hypocalcemia (87.5% vs 16.6%). Hypocalcemia was significantly higher in patients with vitamin D deficiency (p:0.001). In patients with vitamin D deficiency, 87.5% grade1, 8.3% grade 2 and 4.1% grade 3 hypocalcemia developed.

Conclusion: Vitamin D should be checked before treatment to prevent denosumab-related hypocalcemia. New studies should be planned for this recommendation to be in the denosumab PI.

Keywords: Denosumab, hypocalcemia, prostate cancer, vitamin D

Cite This Article: *Gokcen Demiray A, Yaren A, Yapar Taskoylu B, Degirmencioglu S, Gokoz Dogu G, Cakiroglu U, et al. Should Vitamin D Level be Measured Before Denosumab in Patients with Castration-Resistant Metastatic Prostate Cancer to Prevent Hypocalcemia? EJMI 2021;5(3):313–316.*

Prostate cancer is the second most common cancer among men. Bone metastasis are common with castration-resistant metastatic prostate cancer. Pathological fractures, spinal cord compression, and radiotherapy or surgery to the bone are all called skeletal-related events (SREs), which cause severe pain, increase hospitalization rates, morbidity, mortality and impair the quality of life of patients with bone metastases. Treatment with denosumab, a receptor activator of nuclear factor-kappa β ligand inhibitor, reduces SRE with castrate-resistant prostate cancer.[1] Denosumab is more effective than zoledronic acid, with a lower SRE incidence and a delayed onset to first SRE. The benefit of denosumab is considered to be due to its more potent suppression of bone remodelling compared to zoledronic acid, but this may also contribute to an increased risk of hypocalcaemia.[2]

The FDA has approved the use of denosumab 120 mg four weekly for the prevention of SREs in patients with bone metastases from solid tumours. This dose is significantly higher than the usual dose for management of osteoporosis (60

Address for correspondence: Atike Gokcen Demiray, MD. Pamukkale Universitesi Tip Fakultesi, Tibbi Onkoloji Anabilim Dali, Denizli, Turkey
Phone: +90 542 527 39 87 **E-mail:** gokcenakaslan@gmail.com

Submitted Date: May 17, 2021 **Accepted Date:** August 02, 2021 **Available Online Date:** September 22, 2021

mg every 6 months). The inherent risk for hypocalcaemia due to osteoblastic bone metastases and the potent anti-resorptive effect of denosumab render this population particularly at high risk for developing hypocalcaemia.[3]

It is recommended to give calcium and vitamin D as needed to prevent hypocalcemia after denosumab. However, there is no recommendation to check vitamin D level and the specific level of vitamin D that should not be given before denosumab. Even in order to prevent delay in denosumab treatment, studies should be carried out to adjust the dose of denosumab according to the current vitamin D level.

Methods

This retrospective study was approved by the Pamukkale University, Clinical Trials Ethics Committee (Decree No: /29697/ Date: May 12, 2020). We analyzed 40 castration-resistant metastatic prostate cancer patients who received subcutaneous injections of 120 mg denosumab for bone metastases. Patients were eligible for the study if they had been checked for 25 OH D vitamin, serum calcium concentrations before and after the administrations of denosumab. Patients' sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS), serum albumin, serum calcium, serum phosphate, serum magnesium, serum alkaline phosphatase (ALP), parathyroid hormone (PTH) and glomerular filtration rate (GFR) were collected from the medical record. Serum calcium concentration was corrected by albumin. The reference ranges are 8.4-9.7mg/dL for corrected calcium, Hypocalcaemia can range in severity from mild asymptomatic cases to acute life-threatening crises; the Common Terminology Criteria for Adverse Events (CTCAE) define grades of hypocalcaemia from mild (grade 1) to severe (grade 5). Vitamin D deficiency is defined below 20 ng/ml, and insufficiency is defined 21–29 ng/ml. Patients with below 10 ng/ml can be considered to be severely deficient.

Statistical analysis was performed using the Statistical Package for Social Sciences version 22.0. Descriptive statistics were expressed as number and mean±standard deviation. Regression analysis was used to determine the factors affecting SRE, the time of first SRE, and bone progression. The relationship of variables to each other was examined by Pearson Correlation Coefficient.A p value of <0.05 was considered statistically significant.

Results

The mean age was 68±7.2 years. All patients performed well (ECOG PS <2) and had bone metastases of 3 or more. Serum corrected calcium, albumin, phosphate, magnesium, PTH, ALP and GFR measured before treatment were normal. There was no known and detected renal failure, cachexia, gastrointestinal malfunction, gastrectomy history, osteoporosis, previous bisphosphonate use, and secondary cancer. 28 patients had vitamin D deficiency before treatment. Vitamin D level was 10-20 ng/ml in 19 of 28 patients, and vitamin D level was <10 ng/ml in 9 of them. Of the 9 patients with a vitamin D level of <10, grade 3 hypocalcemia developed in 1 patient, grade 2 hypocalcemia in 2 patients, and grade 1 hypocalcemia in 6 patients. Grade 1 hypocalcemia developed in 15 of 19 patients with a vitamin D level of 10-20 ng/ml. Hypocalcemia was observed after densoumab in 65% (n=26) of patients. Patients with vitamin D deficiency had a higher rate of developing hypocalcemia (%87.5 vs %16.6). Hypocalcemia was significantly higher in patients with vitamin D deficiency (p=0.001). In patients with vitamin D deficiency, 87.5% grade1 hypocalcemia, 8.3% grade 2 hypocalcemia and 4.1% grade 3 hypocalcemia developed. Hypocalcemia was seen mostly after the first denosumab cycle. 26 patients presented with hypocalcemia on median 18 days (6-39) after the first (n=23) and second (n=3).

The number of cycles in which denosumab can be given in patients with vitamin D deficiency was less than the others, but it was not statistically significant (p=0.103). No relationship was found between vitamin D deficiency and SRE, the time of first SRE, and bone progression. And also,no relationship was found between the development of hypocalcemia due to vitamin D deficiency and SRE, the time of first SRE, and bone progression. Patient characteristics according to vitamin D levels are summarized in Table 1.

Table 1. Patient characteristics according to vitamin D levels

	25 OH D vitamin		
	≤20 ng/ml (n=28)	20-30 ng/ml (n=8)	≥30 ng/ml (n=4)
Hypocalcemia	24	2	0
Grade 1	21	2	0
Grade 2	2	0	0
Grade 3	1	0	0
Timing of occurrence of hypocalcemia			
1st cycle	21	2	0
2nd cycle	3	0	0
3rd cycle	0	0	0
SRE*	8	4	3
Time to first SRE*, month	6	8	8
Denosumab duration of cycles (median)	12	18	22
Bone progression	6	6	3

SRE: Skeletal-related event.

All patients were asymptomatic, including the patient with grade 3 hypocalcemia.

Discussion

In the phase III trial including patients with metastatic castration-resistant prostate cancer, 13% of patients receiving denosumab showed some degree of hypocalcemia with 5% of them developing grade 3 or higher hypocalcemia Hypocalcaemia occur within the first 6 months of treatment in 82 patients (68%) on denosumab and most events were asymptomatic. No adverse events of hypocalcaemia were fatal. Grade 3 or more hypocalcemia occurred in 48 patients (5%) receiving denosumab.[4] A clinical review identified 20 published cases with prostate cancer with denosumab-associated hypocalcemia. Nine of the 20 patients had vitamin D deficiency (25-OH vitamin D <50 nmol/L) and nine had evidence of renal impairment. Symptoms and signs attributable to hypocalcaemia were present in only seven of the 20 cases. In 13 cases, the hypocalcaemia was asymptomatic.[5]

A case series of 60 patients with metastatic castration-resistant prostate cancer at Memorial Sloan Kettering Cancer Center, 9 (15%) patients had severe hypocalcaemia due to denosumab requiring hospitalisation or intravenous calcium supplementation. Three of the nine patients had vitamin D deficiency, values less than 20 ng/mL. So, it was found that vitamin D deficiency appears to be a significant risk factor for developing denosumab-associated hypocalcaemia.[6]

Retrospective trial data showed that vitamin D and/or calcium supplementation decreases the risk of denosumab associated hypocalcaemia (HR 0.60; 95% CI 0.45 to 0.81; p=0.0007).[7] Other case reports in literature also highlight that low vitamin D levels are likely to predispose patients to develop hypocalcaemia.[8,9]

Real-world data suggest that the incidence of hypocalcaemia associated with denosumab may be higher than has been reported in clinical trials. Retrospective studies of patients treated with denosumab have reported an incidence of 9–22% for hypocalcaemia of grade 2 or higher.[10] The higher incidence of hypocalcaemia encountered in real-world studies compared with clinical trials may reflect poor adherence to guidelines for monitoring of patients in clinical practice. Phase III clinical trials has identified several factors that increase the risk of hypocalcaemia.[7] Hypocalcaemia in patients with cancer frequently relates to a poor nutritional status, and these often have low vitamin D concentrations. Moreover, vitamin D deficiency is associated with an increased risk of hypocalcaemia following treatment with inhibitors of bone resorption and is common in elderly people and those with cancer. Hence, vitamin D deficiency is a concern in men with prostate cancer, given that their median age at diagnosis is 66 years. Indeed, more than 40% of men with prostate cancer shown to have vitamin D deficiency (serum calcidiol <20 ng/ml) at the time of diagnosis.[11]

Although hypocalcaemia can occur at any time during therapy, it is most frequently reported within 6 months of treatment initiation and occurs earlier in patients receiving denosumab than zoledronic acid; in phase III trials, the median time to hypocalcaemia of grade 2 or higher was 3.8 months with denosumab and 6.5 months with zoledronic acid7. Similar findings have been reported in real-world studies; a retrospective review of 55 patients with advanced cancer who were receiving denosumab found that, in most patients, hypocalcaemia developed shortly after treatment administration (median 16 days) and after a median of one injection (range 1–14).[12] Another retrospective study, 66 patients with cancer who received a median of 3–6 cycles of denosumab, found that the incidence of hypocalcaemia of any grade was higher during the first course of therapy (16.7%) than in second or later courses (6.1%).[13] However, long-term clinical trial safety data on denosumab in patients with bone metastases from breast cancer or prostate cancer showed that the incidence of hypocalcaemia did not increase with longer exposure to denosumab.[14]

For patients with a substantial tumour burden in the bone (≥3 bone lesions), prophylactic calcium and vitamin D should be prescribed 1 week before starting treatment with denosumab. During this week, patient adherence to and tolerance of these supplements should be assessed.[15]

We would like to underline the importance of checking vitamin D levels prior to administration of denosumab as well as checking serum calcium levels periodically after drug administration. Patients with low vitamin D can develop severe hypocalcemia that can be resistant to treatment.[16] Patients might not always have symptoms of hypocalcemia until the serum calcium falls to dangerously low levels. Our patients did not have any of the classic symptoms of hypocalcemia and presented to the hospital. However, patients often had to come to the hospital to check their calcium levels.This causes an additional economic cost. In our cases, only vitamin D deficiency was one of the risk factors for hypocalcemia, and the rate of hypocalcemia could have been reduced if it had been maintained at normal levels before denosumab. Modifiable risk factors should be corrected before denosumab.

Conclusion

Vitamin D deficiency is one of the risk factors that can cause hypocalcaemia in patients who received denosumab. Even though there is sufficient evidence regarding the associa-

tion of hypocalcaemia related to concomitant vitamin D deficiency in patients receiving denosumab. Current guidelines still do not recommend checking vitamin D level before denosumab administration. Our study highlights the need to check for vitamin D deficiency prior to denosumab.

Disclosures

Ethics Committee Approval: This retrospective study was approved by the Pamukkale University, Clinical Trials Ethics Committee (Decree No: /29697/ Date: May 12, 2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.G.D.; Design – A.Y.; Supervision – G.G.D.; Materials – S.D., B.Y.T.; Data collection &/or processing – U.C., N.O., C.K.; Analysis and/or interpretation – A.G.D., B.C.D.; Literature search – A.G.D., T.D., M.O.; Writing – A.G.D.; Critical review – A.Y.

References

1. Yerram P, Kansagra S, Abdelghany O. Incidence of hypocalcemia in patients receiving denosumab for prevention of skeletal- related events in bone metastasis. J Oncol Pharm Pract 2017;23:179–84. [CrossRef]
2. Koguchi D, Satoh T, Tsumura H, Tabata K, Oyama T, Ishikawa W, et al. Risk factors for hypocalcemia following treatment with denosumab in patients with bone metastases from prostate cancer. J Clin Trials 2016;6:1–7. [CrossRef]
3. Gunawan F, George E, Kotowicz M. Denosumab-induced hypocalcaemia in metastatic castrate-resistant prostate cancer. Endocrinol Diabetes Metab Case Rep 2019;2019:19–0063.
4. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, 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;377:813–22.
5. Lau LH, Cliff ERS, Wong V, Wong H, Torkamani N, Eer A, et al. Hypocalcaemia following denosumab in prostate cancer: A clinical review. Clin Endocrinol (Oxf) 2020;92:495–502. [CrossRef]
6. Autio KA, Farooki A, Glezerman IG, Chan A, Schneider CW, Barr HC, et al. Severe hypocalcemia associated with denosumab in metastatic castration-resistant prostate cancer: risk factors and precautions for treating physicians. Clin Genitourin Cancer 2015;13:305–9. [CrossRef]
7. Body JJ, Bone HG, de Boer RH, Stopeck A, Van Poznak C, Damião R, et al. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. Eur J Cancer 2015;51:1812–21.
8. Ali N, Farhat S, Imran S, Jafri M, Ahmed A, Malik F. Severe refractory hypocalcemia in a patient with metastatic prostate carcinoma following denosumab injection. J Clin Case Rep 2016;6:1–3. [CrossRef]
9. Watthanasuntorn K, Abid H, Gnanajothy R. Severe hypocalcaemia following denosumab in a patient with cancer with vitamin D deficiency. BMJ Case Rep 2018;11:e226727. [CrossRef]
10. Huynh AL, Baker ST, Stewardson AJ, Johnson DF. Denosumab-associated hypocalcaemia: incidence, severity and patient characteristics in a tertiary hospital setting. Pharmacoepidemiol Drug Saf 2016;25:1274–8. [CrossRef]
11. Droz JP, Albrand G, Gillessen S, Hughes S, Mottet N, Oudard S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the International Society of Geriatric Oncology. Eur Urol 2017;72:521–31. [CrossRef]
12. Lechner B, DeAngelis C, Jamal N, Emmenegger U, Pulenzas N, Giotis A, et al. The effects of denosumab on calcium profiles in advanced cancer patients with bone metastases. Support Care Cancer 2014;22:1765–71. [CrossRef]
13. Ikesue H, Tsuji T, Hata K, Watanabe H, Mishima K, Uchida M, et al. Time course of calcium concentrations and risk factors for hypocalcemia in patients receiving denosumab for the treatment of bone metastases from cancer. Ann Pharmacother 2014;48:1159–65. [CrossRef]
14. Stopeck AT, Fizazi K, Body JJ, Brown JE, Carducci M, Diel I, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer 2016;24:447–55 [CrossRef]
15. Body JJ, von Moos R, Niepel D, Tombal B. Hypocalcaemia in patients with prostate cancer treated with a bisphosphonate or denosumab: prevention supports treatment completion. BMC Urol 2018;18:81. [CrossRef]
16. Imatoh T, Sai K, Takeyama M, Hori K, Karayama M, Furuhashi K, et al. Identification of risk factors and development of detection algorithm for denosumab-induced hypocalcaemia. J Clin Pharm Ther 2019;44:62–8. [CrossRef]