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Risk Factors for Hypocalcemia following Treatment with Denosumab in Patients with Bone Metastases from Prostate Cancer

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Abstract

Objective: To evaluate risk factors for Denosumab-induced hypocalcemia in prostate cancer patients with bone metastases.

Methods: In this single-arm, open-label, prospective multicenter study, 48 prostate cancer patients with bone metastases received Denosumab (120 mg on day 1) and androgen-deprivation therapy. Serum calcium, albumin, alkaline phosphatase (ALP), and phosphate levels; chronic kidney disease stage; and serum prostate specific antigen and urine N-terminal telopeptide (u-NTx) levels were examined. Patients were divided into 2 groups on the basis of whether or not they developed hypocalcemia at 1 week or 1 month after Denosumab administration. Risk factors for hypocalcemia were determined by univariate and multivariate logistic regression analysis.

Results: Nineteen patients (39.6%) demonstrated hypocalcemia at 1 week after Denosumab administration, and 16 (33.3%) were hypocalcemic at 1 month. Patients with hypocalcemia at 1 week had higher baseline serum ALP levels (1283.4 ± 1489.7 [mean ± SD] vs 467.3 ± 655.8, P=0.013) than patients without hypocalcemia. Patients with hypocalcemia at 1 month had higher baseline serum ALP (1455.5 ± 1694.1, P=0.002) and u-NTx levels (190.9 ± 63.9, P=0.013) and more bone metastases (extent of disease grade ≥ 3; 10 patients, 20.8%, P=0.006) at baseline than patients without hypocalcemia. Multivariate logistic regression analysis revealed that baseline u-NTx of >100 nmol bone collagen equivalents/mmol creatinine was a significant independent risk factor for hypocalcemia (odds ratio=12.41, 95% confidence interval=1.059-145.600, P=0.049).

Conclusions: Baseline u-NTx level is an independent risk factor for Denosumab-induced hypocalcemia in prostate cancer patients with bone metastases.

Keywords: Prostate cancer; Bone metastasis; Denosumab; Hypocalcemia

Abbreviations

PSA: Prostate Specific Antigen; CRPC: Castration-Resistant Prostate Cancer; NTx: N-Terminal Telopeptide; BCE: Bone Collagen Equivalents; Cr: Creatinine; ALP: Alkaline Phosphatase; P: Phosphate; EOD: Extent of Disease; CKD: Chronic Kidney Failure; OR: Odds Ratio; CI: Confidence Interval; SREs: Skeletal-Related Events; CCR: Creatinine Clearance

Introduction

Prostate cancer is diagnosed in more than 670,000 men yearly worldwide [1,2], and compared to other malignancies, urological malignancies are the most common cause of bone metastases (70–80%) [3,4]. Patients with bone metastases may experience local irreversible skeletal complications, including pathologic fractures and spinal cord compression, and may require bone irradiation or surgery. Such complications, referred to as skeletal-related events (SREs), are indicators of poor prognosis and cause substantial pain and morbidity that frequently lead to hospitalization, poor quality of life, and increased utilization of medical resources [5-9]. In recent decades, patients with metastatic castration-resistant prostate cancer have been living longer, owing to the advent of newer, targeted therapies [10,11]. Therefore, they are more likely to experience SREs and the role of bone-targeted therapies to prevent and treat SREs is becoming more important.

The functional mechanism of Denosumab differs from that of bisphosphonates, which have been the first-line choice for prevention of SREs for more than a decade. Denosumab, a fully human monoclonal antibody with high affinity and specificity for the human receptor activator of nuclear factor-κB ligand, was shown to inhibit bone re-absorption in early studies in patients with advanced cancer, including those who did not respond to prior bisphosphonate treatment [12-15], and these results suggest a potential new approach for the treatment of bone metastasis. However, according to drug safety information released by the European Medicines Agency [16], hypocalcemia can occur at any time during Denosumab therapy but occurs most commonly within the first 6 months of therapy. Patients

with severe renal impairment (creatinine clearance of <30 ml/min) or who are on dialysis are at greater risk of developing hypocalcemia. The United States Food and Drug Administration released prescribing information indicating that Denosumab can cause severe symptomatic hypocalcemia, and fatal cases have been reported [17]. In addition, the Japanese Ministry of Health, Labour and Welfare called attention to serious hypocalcemia resulting from Denosumab administration [18]. However, information about the incidence of and risk factors for hypocalcemia associated with Denosumab treatment is limited. In this study, we evaluated the risk factors for the development of hypocalcemia after treatment with Denosumab for the prevention of skeletal complications in prostate cancer patients with bone metastases.

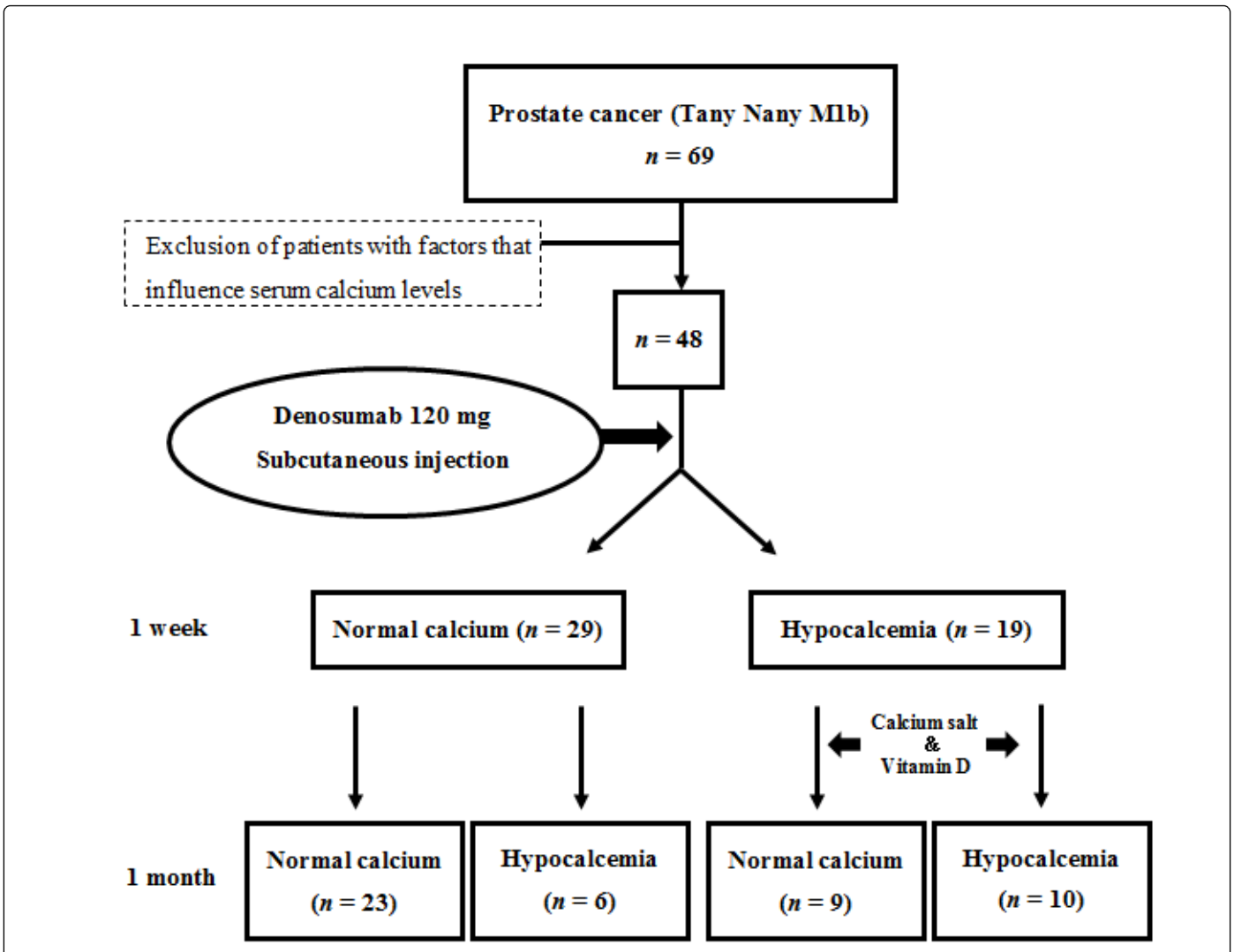

Figure 1: Study design. Sixty-nine patients with radiologically documented bone metastases from prostate cancer who were treated with androgen-deprivation therapy and denosumab (120 mg) were analyzed. Patients who received medicines that affect serum calcium levels or who had a history of parathyroid disorder or hypercalcemia were excluded from the study (n=29). The remaining 48 patients were divided into 2 groups on the basis of whether hypocalcemia developed at 1 week after the administration of denosumab. Then at 1 month after the administration, patients were divided into 2 groups on the basis of whether hypocalcemia developed. During the observation period, vitamin D and calcium supplements were initiated soon after hypocalcemia (any grade) was detected, and denosumab was withdrawn until the serum calcium level returned to the normal range.

Patients and Methods

Patients

We analyzed data for 69 consecutive patients who had radiologically documented bone metastases from prostate cancer and who were treated with initial subcutaneously injected Denosumab (120 mg) on day 1 at Kitasato University Hospital or Sagamidai Hospital from May 2012 to May 2013.

Patients were excluded if they were receiving calcitonin hydrochloride, thalidomide, a calcium salt, vitamin D, or vitamin K or if they had a history of parathyroid disorder or hypercalcemia (adjusted serum calcium concentration of >10.2 mg/dl) before administration of Denosumab. A total of 48 patients were deemed eligible for the study (Figure 1).

The study protocol and informed consent documents were reviewed and approved by an Institutional Review Board of Kitasato University Hospital and Sagamidai Hospital. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, in accordance with ICH Good Clinical Practice guidelines and with applicable regulatory requirements, and in compliance with the protocol.

Study design

This study was a single-arm, open-label, prospective multicenter study of patients with prostate cancer with bone metastases. Forty-eight eligible patients received Denosumab injected subcutaneously at a dose of 120 mg on day 1. Androgen-deprivation therapy was used in all cases. During the observation, vitamin D and calcium supplements were introduced as soon as any grade of hypocalcemia was found and the drug had been withdrawn until serum calcium level returned to normal range (Figure 1).

Study endpoints and evaluations

The primary endpoint was the occurrence of hypocalcemia 1 week and 1 month after the administration of Denosumab. Then risk factors for Denosumab-induced hypocalcemia in patients with bone metastases from prostate cancer were evaluated.

The following patient characteristics and laboratory data were collected at baseline: age at the start of Denosumab treatment; Gleason score; androgen sensitivity status (castration-resistant prostate cancer or not); history of treatment or prevention of SREs (zoledronic acid hydrate or none); serum concentrations of calcium, albumin alkaline phosphatase (ALP), phosphate and prostatic specific antigen (PSA); urine N-terminal telopeptide (uNTX) level; extent of disease (EOD; i.e., extent of bone metastasis on initial bone scan); and chronic kidney disease (CKD) stage. The EOD was classified by the method of Soloway et al. [19]: EOD 0, normal; EOD 1, bone metastases, <6 lesions; EOD 2, bone metastases, 6–20 lesions; EOD 3, bone metastases, >20 but less than superscan; and EOD 4, superscan (75% of ribs, vertebrae, and pelvic bones had lesions). CKD was classified according to the guidelines introduced by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative in 200220). Then serum concentrations of calcium, albumin, ALP and phosphate were monitored 1 week and 1 month after the admistration of Denosumab. Urine NTx and serum PSA were examined 1 month after that.

If the serum albumin level was less than 4.0 mg/dl, an adjusted serum calcium level was calculated according to the following equation: adjusted serum calcium level=serum calcium level (mg/dl) +4.0-serum albumin level (mg/dl). Serum calcium level was assessed according to the National Cancer Institute Common Toxicity Criteria (ver. 4.0); the two institutes set the lower limit of normal for serum calcium as 8.8 mg/dl and the upper limit as 10.2 mg/dl.

Statistical analysis

Data are reported as number of patients and percentage or as median or mean. At 1 week after Denosumab administration and again at 1 month after Denosumab administration, patients were divided into 2 groups on the basis of whether or not hypocalcemia had developed. The t test was used for 2-group comparisons with respect to age; serum PSA, calcium, ALP, and phosphate levels; and u-NTx level. Pearson's chi-square test was adopted for comparisons with respect to the number of patients with castration-resistant prostate cancer, with an EOD of ≥ 3, or with a history of receiving zoledronic acid hydrate. The Mann-Whitney U test and the Fisher test were used for comparisons with respect to Gleason score and number of patients with CKD ≥ 3, respectively. In addition, the associations between hypocalcemia caused by Denosumab and various clinical factors were evaluated by means of multivariate logistic regression analysis. Odds ratios and 95% confidence intervals were determined for each factor. A P value of <0.05 was considered statistically significant in all the analyses. Statistical analyses were performed using SPSS statistical software (version 13.0; SPSS Japan Inc., Tokyo, Japan).

Results

Characteristics at baseline of 48 consecutive patients treated with Denosumab were evaluated (Table 1). The mean age was 72.3 years (range 49-89 years). 25% of the patients had CKD ≥ 3, and 37.5% had an EOD of ≥ 3.

Characteristic	Value[a]
Age at start of denosumab treatment, years	72.3 (49-89)
Serum PSA, ng/ml	415.1 (4.04-8278)
Gleason score ≥ 8	36 (75)
CRPC	19 (39.6)
Zoledronic acid hydrate	16 (33)
Serum calcium, mg/dl	9.3 (8.8-10.3)
Urine NTx, nmol BCE/mmol Cr	105.6 (7.4-829.8)
Serum ALP, IU/L	790.3 (150-6073)
Serum P, mg/dl	3.3 (2.0-4.0)
EOD ≥ 3	18 (37.5)
CKD ≥ 3	12 (25)

[a]Unless otherwise stated, values are medians with ranges in parentheses or numbers of patients with percentages in parentheses.

Table 1: Characteristics of patients at baseline (n=48).

Hypocalcemia grade	No. of patients (%)	
	1 week	1 month
Grade 1 (8.0-8.7)	13 (27.1)	13 (27.1)
Grade 2 (7.0-7.9)	6 (12.5)	1 (2.1)
Grade 3 (6.0-6.9)	0	2 (4.2)
Grade 4 (<6.0)	0	0
Grade 5 (death)	0	0
Total (%)	19 (39.6)	16 (33.3)

Table 2: Numbers of patients with hypocalcemia at 1 week and 1 month after denosumab administration, by grade. Table shows that denosumab-induced hypocalcemia occurred soon after its administration and was found in more than one-third of all patients.

The numbers of patients with hypocalcemia at 1 week and 1 month after Denosumab administration are shown in Table 2. Nineteen patients (39.6%) demonstrated hypocalcemia at 1 week and 16 patients

(33.3%) at 1 month. Symptomatic hypocalcemia was not found in any of the patients.

The patients with hypocalcemia at 1 week after Denosumab administration had higher baseline serum ALP than the patients who did not have hypocalcemia at 1 week (658 ± 1694.1 [mean ± SD] vs. 339 ± 0.4). Univariate logistic regression analysis of data obtained at 1 week after the administration of Denosumab demonstrated that a baseline u-NTx level of ≥ 100 nmol bone collagen equivalents /mmol creatinine (nmol BCE/mmol Cr) and a baseline serum ALP level of ≥ 500 IU/L were significant risk factors for hypocalcemia (odds ratio [OR]=7.875, 95% confidence interval [CI]=1.421-43.640 and OR=10.710, 95% CI=2.620-43.810, respectively). Multivariate logistic regression analysis showed that a baseline serum ALP level of ≥ 500 IU/L was an independent risk factor for hypocalcemia at 1 week after the administration of Denosumab (OR=7.596, 95% CI=1.542-37.410).

At 1 month after Denosumab administration, compared to patients who did not have hypocalcemia, patients who did have hypocalcemia had higher baseline serum ALP and baseline u-NTx (1455.5 ± 1694.1 [mean ± SD] vs.190.9 ± 63.9, respectively). In addition, the percentage of patients with EOD of ≥ 3 at baseline was higher in the hypocalcemic group than in the non-hypocalcemic group (10 patients [62.5%] vs 8 patients [25.0%]). Univariate logistic regression analysis of the data at 1 month after Denosumab administration demonstrated that a u-NTx level of ≥ 100 nmol BCE/mmol Cr, a serum ALP level of ≥ 500 IU/L, and an EOD of ≥ 3 were significant risk factors for hypocalcemia (OR=31.000, 95% CI=3.368–285.300; OR=7.222, 95% CI=1.879-27.750; and OR=5.000, 95% CI=1.376-18.170, respectively). Upon multivariate analysis, only a u-NTx level of ≥ 100 nmol BCE/mmol Cr was an independent risk factor for hypocalcemia (OR=12.410, 95% CI=1.059-145.600).

In patients with grade 2 or 3 hypocalcemia at either 1 week or 1 month after Denosumab administration (8 patients, 16.7%), serum calcium levels returned to the normal range within 1 to 4 months after Denosumab administration (Figure 2). The median time from first observation of hypocalcemia to return to the normal range was 42 days (range 28-105 days).

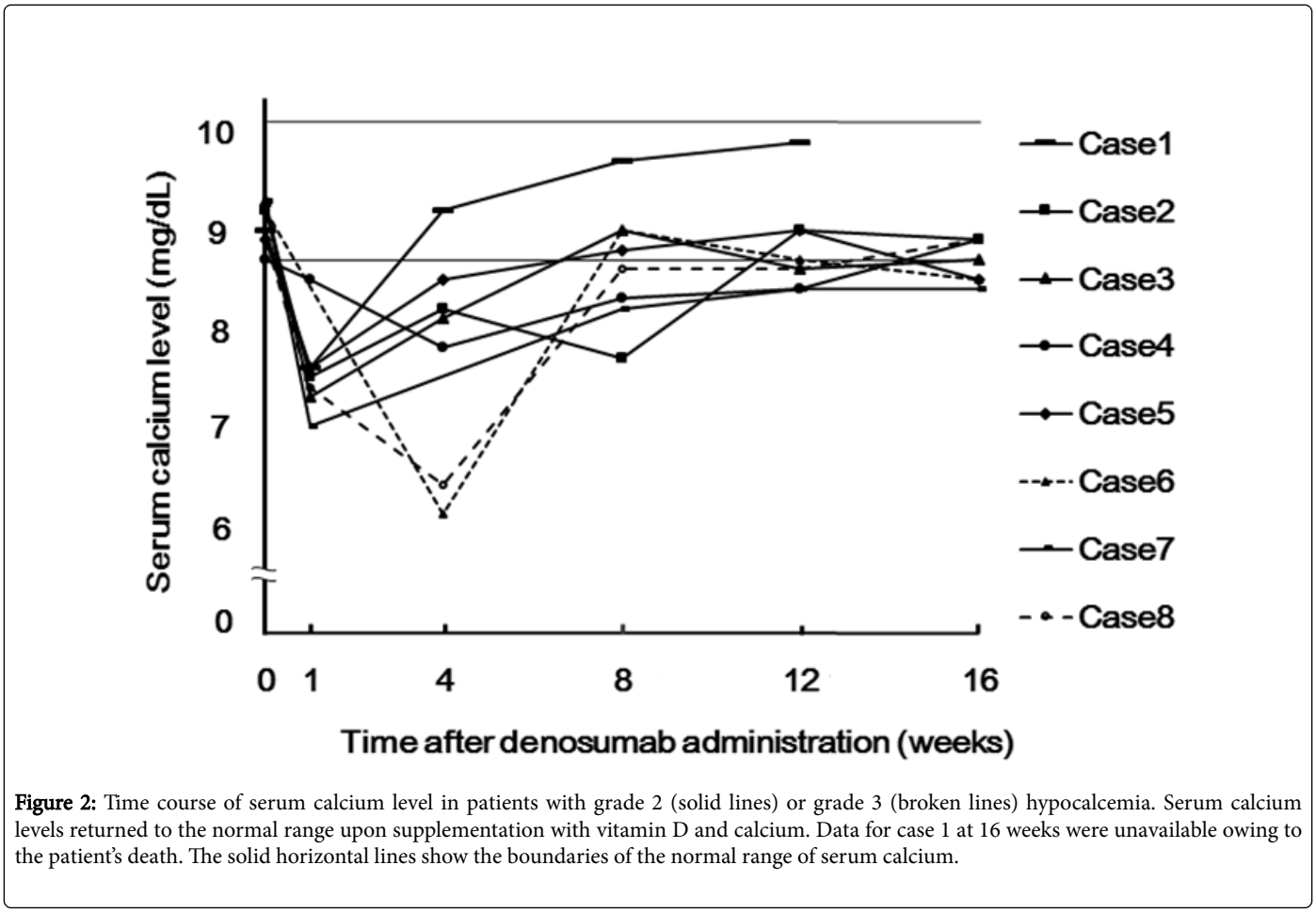

Figure 2: Time course of serum calcium level in patients with grade 2 (solid lines) or grade 3 (broken lines) hypocalcemia. Serum calcium levels returned to the normal range upon supplementation with vitamin D and calcium. Data for case 1 at 16 weeks were unavailable owing to the patient's death. The solid horizontal lines show the boundaries of the normal range of serum calcium.

Discussion

Hypocalcemia is a common adverse effect of bone-modifying agents such as bisphosphonates and Denosumab [20-22]. In a randomized phase 2 study of Denosumab and a bisphosphonate (pamidronate or zoledronic acid) in patients with multiple malignancies with bone involvement, 6 of 74 patients (8%) treated with Denosumab developed grade 3 hypocalcemia, and 1 patient (1%) developed grade 4 hypocalcemia; in contrast, there was only 1 patient with grade 3 hypocalcemia among 37 patients (3%) treated with a bisphosphonate [14]. In a phase 3 trial comparing Denosumab with zoledronic acid, hypocalcemia developed in 13% of patients on Denosumab and in 6% of patients on zoledronic acid; grade 3 hypocalcemia occurred in 5% and 1% of the Denosumab and zoledronic acid groups, respectively [23]. The results of these randomized control trials indicate that Denosumab use may increase the risk of hypocalcemia more than bisphosphonate use.

Recently, Lechner et al., [21] retrospectively examined the incidence and management of hypocalcemia among patients with bone

metastases treated with Denosumab. As indicated by Common Terminology Criteria for Adverse Events grading, 17 (32.7%) patients experienced up to grade 1 hypocalcemia, 4 (7.7%) patients experienced up to grade 2 hypocalcemia, 4 (7.7%) patients experienced up to grade 3 hypocalcemia, and 1 (2.9%) patient experienced up to grade 4 hypocalcemia. In our study of Japanese patients, 39.6% developed hypocalcemia of grade 1 or greater after Denosumab administration. The incidence of hypocalcemia in the Japanese patients in our study was higher than that in previously reported randomized control trials [14,23] and close to that reported by Lechner et al., indicating that in standard practice, patients with bone metastases may have a higher likelihood of developing hypocalcemia.

As reported by the US Food and Drug Administration [17], an increased risk of hypocalcemia has been observed in clinical trials of patients with renal dysfunction, and the risk is particularly high among patients with severe dysfunction (that is, patients with a creatinine clearance of <30 ml/min or who were on dialysis). The Japanese Ministry of Health, Labour and Welfare [18] has reported that patients with severe renal dysfunction have an increased risk of hypocalcemia after Denosumab injection. However, the risk factors for the development of hypocalcemia following Denosumab in patients with bone metastases have not been studied in detail. In a retrospective review of the records of patients who had received Denosumab, univariate logistic regression analysis illuminated that the patients without a history of receiving zoledronic acid before Denosumab or with low creatinine clearance (CCr) were found to have a high risk of hypocalcemia (P=0.040 and 0.030, respectively) [24]. The cut off value of CCr was 50.4 mL/min calculated by receiver-operator characteristics curves. Furthermore, multivariate logistic regression analysis showed that non-administration of zoledronic acid (OR=10.430, P =0.040) and CCr less than 50.0 ml/min (OR= 5.900, P=0.040) were independent risk factors for hypocalcemia caused by Denosumab.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age, years	1.019	0.953-1.088	0.584			
Serum PSA, ng/ml	0.999	0.998-1.001	0.484			
Gleason score ≥ 8	2.4	0.556-10.36	0.24			
CRPC	0.826	0.251-2.715	0.753			
Zoledronic acid hydrate	0.877	0.255-3.012	0.834			
Serum calcium <9.0 mg/dl	1.667	0.362-7.672	0.511			
Urine NTx ≥ 100 nmol BCE/mmol Cr	7.875	1.421-43.64	0.018	2.316	0.300-17.86	0.42
Serum ALP ≥500 IU/L	10.71	2.620-43.81	0.01	7.596	1.542-37.41	0.012
EOD ≥ 3	2.917	0.866-9.823	0.08			
CKD ≥ 3	0.224	0.043-1.168	0.075			

Table 3: Logistic regression analysis of risk factors for denosumab-induced hypocalcemia at 1 week after administration.

Chronic renal failure with a reduction in glomerular filtration rate may present with decreased production of 1,25-dihydroxyvitamin D, and absorption of calcium in the enteron can be reduced owing to the inactivation of vitamin D. However, in our study, low CCr did not correlate with an increased risk of hypocalcemia. Therefore, although renal dysfunction may be a risk factor for hypocalcemia, it may not be a strong risk factor compared to massive bone metastatic burden that was often observed in patients with elevated bone turnover as our multivariate analysis results revealed that u-NTx level was a significant independent risk factor for the development of hypocalcemia.

The body calcium pool is made up of the plasma calcium in rapid exchange largely with the calcium in bone mineral [25], and this dynamic equilibration verges to bone mineral under accelerated bone metabolism. In patients with elevated bone turnover, we believe that Denosumab administration rapidly suppresses bone turnover, and the result is a decrease in the supply of calcium to the plasma from bone. In fact, the results of the present study demonstrates that pretreatment factors of a serum ALP level of ≥ 500 IU/ml, an EOD of ≥ 3, and a u-NTx level of ≥ 100 nmol BCE/mmol Cr were positively correlated with hypocalcemia induced by Denosumab (Tables 3 and 4). Therefore, massive bone metastatic burden may affect serum calcium homeostasis after Denosumab administration. However, serum calcium levels recovered to normal in all cases within 16 weeks (Figure 2). This finding indicates that early monitoring of serum calcium is crucial for determining whether the continued use of Denosumab is safe.

The timing of the occurrence of hypocalcemia after Denosumab administration is becoming clearer. Lechner et al., [21] reported the median time from the first Denosumab injection to the occurrence of grade 2 hypocalcemia was 16 days. We found that 8 patients developed grade 2 or 3 hypocalcemia during the study period, and among these, 6 patients (75%) had confirmed hypocalcemia at 1 week after Denosumab administration. This is a key point for clinicians; that is, our findings suggest that calcium levels should be monitored not only before the first administration but also in the early phase of treatment, especially at around 1 week after the first dose of Denosumab.

The current study had some limitations. First, prophylactic administration of calcium and vitamin D supplements was not covered by health insurance in Japan during the study period, and this fact might have resulted in a high incidence of hypocalcemia. Second, the sample size was relatively small, and there was only a single arm. Large-scale prospective trials are needed.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age, years	1.017	0.950-1.090	0.62			
Serum PSA, ng/ml	1	0.998-1.001	0.528			
Gleason score ≥ 8	1.696	0.389-7.398	0.482			
CRPC	0.877	0.255-3.012	0.834			
Zoledronic acid hydrate	1.988	0.568-6.958	0.285			
Serum calcium <9.0 mg/dl	0.619	0.110-3.483	0.586			
Urine NTx ≥ 100 nmol BCE/mmol Cr	31	3.368-285.3	0.002	12.41	1.059-145.6	0.049
Serum ALP ≥ 500 IU/L	7.222	1.879-27.75	0.004	2.514	0.466-13.57	0.283
EOD ≥ 3	5	1.376-18.17	0.014	2.521	0.538-11.81	0.24
CKD ≥ 3	0.314	0.060-1.652	0.171			

Table 4: Logistic regression analysis of risk factors for denosumab-induced hypocalcemia at 1 month after administration.

Conclusion

This is the first report on the risk factors contributing to the development of hypocalcemia after Denosumab administration in patients with bone metastases from prostate cancer. Multivariate analysis revealed that beseline u-NTx level was an independent risk factor for hypocalcemia and that patients with high baseline u-NTx levels should be monitored for hypocalcemia after the first dose of Denosumab.

Conflict of Interest

The authors declare the following financial potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Satoh received speaking fees from Daiichi Sankyo Co Ltd., Astra Zeneca, and Janssen Pharmaceutical K.K.

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