Risk Analysis of Denosumab-Induced Hypocalcemia in Bone Metastasis Treatment: Renal Dysfunction Is Not a Risk Factor for Its Incidence in a Strict Denosumab Administration Management System with Calcium/Vitamin D Supplementation

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We have reported that a strict denosumab administration management system with oral calcium/vitamin D supplementation attenuates denosumab-induced hypocalcemia in 158 cancer patients with bone metastasis. In this report, 27.8% of the patients experienced hypocalcemia, including 0.6% with grade 2. So far, the risk factors for ≥ grade 2 hypocalcemia incidence have been identified in denosumab-treated cancer patients, including patients without calcium/vitamin D supplementation. Therefore, the present study aimed to reveal the factors that affect all-grade hypocalcemia incidence with calcium/vitamin D supplementation and team medical care according to the management system. A receiver operating characteristic curve analysis suggested that the cutoff of baseline serum calcium level for all-grade hypocalcemia incidence was 9.3 mg/dL. Multivariate analysis revealed that age ≥ 65 years (odds ratio, 95% confidence interval: 2.57, 1.11–5.95, p = 0.03), grade 1 or higher serum alkaline phosphatase elevation (3.70, 1.71–8.00, p < 0.01), an adjusted serum calcium level of less than 9.3 mg/dL (3.21, 1.25–8.24, p = 0.02) at baseline, and co-administration of cytotoxic agents (2.33, 1.06–7.11, p = 0.03) are risk factors for the incidence of all-grade hypocalcemia. However, renal dysfunction, which has been suggested to be a risk factor in previous reports, was not a factor. In conclusion, we revealed the risk factors for all-grade hypocalcemia in calcium/vitamin D supplementation and awareness, as demonstrated by the management system. Moreover, renal dysfunction was not a risk factor in our strict denosumab administration management system. Our results support the value of early detection of hypocalcemia incidence to guide the selection of an appropriate management strategy.

Key words denosumab; hypocalcemia; pharmaceutical management; calcium supplementation; risk factor; renal dysfunction

INTRODUCTION

Bone metastasis occurs in conjunction with malignancies, such as breast, prostate, thyroid, lung, and kidney. 1) It significantly reduces patient’s QOL due to pain developed in 60–70% of patients 2) and local irreversible skeletal-related events (SREs). 3)

Denosumab is a fully monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL) 4) and prevents SRE occurrence, and attenuates or avoids the associated pain. Hypocalcemia is the most typical adverse effect caused by denosumab, 5) and occurs in 5–50% of patients. 6–7) As it is life-threatening in severe cases, we developed a strict management system to achieve more efficient and safer management of denosumab administration for bone metastasis. 8) (Fig. 1).

The risk factors for the incidence of grade 2 or more hypocalcemia are reported to be prostate cancer, small cell lung carcinoma, gastric cancer, poor performance status (PS), higher baseline value of the urinary N-telopeptide of type I collagen (uNTx), bone-specific alkaline phosphatase (BSAP), higher serum alkaline phosphatase (ALP), and renal dysfunction. 6–9, 30) Calcium supplements are known to prevent hypocalcemia 5); therefore, calcium/vitamin D supplementation is strongly recommended with denosumab treatment. In the studies described above, risk analysis was conducted for ≥ grade 2 hypocalcemia incidence, and not all patients were administered calcium/vitamin D supplementation. However, in our previous study, patients were administered the supplements according to the dose adjustment guideline in the system, and severity of hypocalcemia with our effort was milder than that of previous reports, 9) as ≥ grade 2 hypocalcemia incidence was just 0.6%. However, there are still approximately 30% of patients experiencing this symptom. There are some cases that display a gradual decrease following each administration, and patients with grade 1 hypocalcemia are at a risk of further degradation. Therefore, we considered that the elucidation of risk factor(s) for all-grade hypocalcemia with calcium/vitamin D supplementation and operation of the management system would be useful for synthesizing a further approach. This study aimed to reveal the factors that affect all-grade hypocalcemia incidence with calcium/vitamin D supplementation and team medical care according to the management system.

MATERIALS AND METHODS

Patients and Denosumab Administration Patient selection was previously reported. 30) Briefly, patients who were administered denosumab for bone metastasis treatment for 6 months or more from April 2016 to March 2020 at Hokkaido University Hospital were retrospectively assessed. Denosumab 120mg was subcutaneously injected every four weeks, and all patients were administered oral calcium/vitamin D supplement medicine (DENOTAS CHEWABLE COMBINATION TABLETS) with the dose adjusted according to the management system from denosumab initiation. 30) Patients whose administration interval of denosumab was more than five weeks and who were previously injected denosumab for osteoporosis and intravenous bisphosphonate were excluded.

The present study was approved by the Institutional Review Board of the Hokkaido University Hospital (Approval No. 020-0096) and was performed in accordance with the Declaration of Helsinki. Given the retrospective nature of the study, informed consent from the subjects was not required.
Evaluation of Denosumab-Induced Hypocalcemia

All required information was obtained from the medical records of patients. The evaluation period was defined as 6 months from the initial denosumab administration according to previous reports. The living abilities of patients were evaluated using Eastern Cooperative Oncology Group PS (ECOG PS). The creatinine clearance (CCr) and serum calcium levels were calculated using the Cockcroft and Gault formula and the Payne formula, respectively. The normal range of adjusted serum calcium levels was 8.8–10.1 mg/dL at our facility. The lowest serum calcium level was assessed. The severity of symptoms was evaluated in accordance with the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

A receiver operating characteristic (ROC) curve analysis was used to estimate the optimal cutoff values of the adjusted serum calcium level at baseline for all-grade hypocalcemia incidence. The univariate and multivariate analyses using logistic analysis were carried out to identify the independent risk factors involved in the incidence of all-grade hypocalcemia. Potential risk factors included sex, age, body weight, cancer type (lung or prostate cancer), CCr, liver dysfunction, serum ALP, serum albumin, and adjusted serum calcium level at baseline, and the co-administration of corticosteroids and cytotoxic agents based on reference to previous reports. Variables that had potential associations with developing hypocalcemia, as suggested by univariate logistic regression analysis ($p<0.10$), were considered when building the multivariable model. All analyses were conducted using JMP version 14.0 (SAS Institute Japan, Tokyo, Japan). Differences were considered to be statistically significant when $p$-values were less than 0.05.

RESULTS

Patient Characteristics

The baseline characteristics of patients are presented in Table 1, which were presented in our previous report. There were no patients with hypocalcemia at baseline, and all patients were assessed for PS 0–1. Patients with liver dysfunction totaled 27.8% and patients with CCr $<30$ mL/min, $30 \leq 60$ mL/min, $60 \leq 90$ mL/min, and $>90$ mL/min were 1.2, 16.5, 50.0, and 32.3%, respectively. In addition to the previous results, 13.3% of patients were administered regular corticosteroids and 42.4% were administered cytotoxic agents. All patients were administered DENOTAS CHEWABLE COMBINATION TABLETS $^\circledR$ (2.0 ± 0.49 tablets daily). Calcium lactate (1–3 g/d) was additionally administered in 7 patients (4.4%).

Univariate and Multivariate Analyses of Risk Factors for the Incidence of All-Grade Hypocalcemia

The incidence of hypocalcemia was 27.8% with just one patient in grade 2 as reported previously. The median time of the initial incidence of hypocalcemia was after the second ad-
administration (range, interquartile range; 1–6, 1–3), as well as within the lowest serum calcium level. ROC curve analysis revealed that the cutoff of baseline adjusted serum calcium level was 9.3 mg/dL, with an area under the ROC curve of 0.63 (95% confidence interval (CI): 0.53–0.73), sensitivity of 45.5%, and specificity of 75.4% ($p < 0.01$, Fig. 2). The results of the univariate and multivariate analyses are shown in Table 2. Multivariate analysis revealed that age ≥65 years, grade 1 or higher serum ALP elevation, adjusted serum calcium level <9.3 mg/dL at baseline, and the co-administration of cytotoxic agents are risk factors for all-grade hypocalcemia.

Table 1. Patient Characteristics

| Characteristics                  | Value                        |
|----------------------------------|------------------------------|
| Gender (male/female)             | 93/65                        |
| Age (median, range)              | 67 (26–88)                   |
| Performance status               | 0–1                          |
| Type of primary cancer           |                              |
| Lung                             | 57                           |
| Breast                           | 34                           |
| Prostate                         | 24                           |
| Kidney                           | 9                            |
| Head and neck                    | 8                            |
| Thyroid                          | 6                            |
| Colorectal                       | 5                            |
| Liver                            | 3                            |
| Melanoma                         | 3                            |
| Angiosarcoma, duodenum, endometrial, gastric, multiple myeloma, primary unknown, pancreatic, sarcoma, urothelium | 1 |
| Liver dysfunction*               |                              |
| Body weight (kg) (median, range) | 58.7 (36.0–117.0)            |
| Serum creatinine (mg/dL) (median, range) | 0.72 (0.38–2.13)            |
| Calculated CCr** (mL/min) (median, range) | 78.4 (25.8–210.0)          |
| Number of patients with CCr <30 mL/min | 2                             |
| 30 ≤ 60 mL/min                   | 26                           |
| 60 ≤ 90 mL/min                   | 79                           |
| >90 mL/min                       | 51                           |
| Serum albumin (g/dL) (median, range) | 3.9 (2.6–5.0)                |
| Serum calcium (mg/dL) (median)    | 9.3 (8.1–10.6)               |
| Adjusted serum calcium (mg/dL)    | 9.5 (8.8–11.2)               |
| Co-administration of corticosteroids | 21                        |
| Co-administration of cytotoxic agents | 67                        |

*Liver dysfunction is defined by grade 1 or higher aspartate transaminase, alanine aminotransferase, and total bilirubin elevation. **CCr; creatine clearance. Reproduced from Reference 8.

DISCUSSION

We developed a strict management system of denosumab administration for the prevention of severe hypocalcemia soon after the caution statement published by the Japanese Ministry of Health, Labor and Welfare on September 2012. In the previous report, we revealed that pharmaceutical management according to our system significantly normalize the decreased serum calcium level. In addition, it reduced the severe symptom incidence (≥grade 2 for 0.6%) compared to previous reports (7.7–17.3%). In this study, we assessed the risk factors for all-grade hypocalcemia as there was only one patient with grade 2 incidence to derive a further approach.

Multivariate analysis revealed that age ≥65 years, grade 1 or higher serum ALP elevation, adjusted serum calcium level <9.3 mg/dL at baseline, and the co-administration of cytotoxic agents are risk factors for all-grade hypocalcemia, with calcium/vitamin D supplementation and awareness as demonstrated in the management system. Of them, lower serum calcium level at baseline, older age, and concomitant administration of cytotoxic agents were initially suggested as risk factors. Cytotoxic agents induce nausea, vomiting, and stomatitis, which might have induced dietary intake decrease or made calcium/vitamin D supplementation difficult, leading to hypocalcemia. Moreover, the administration interval of denosumab often differs from that of chemotherapy, which enabled us to detect the lowest serum calcium level via frequent monitoring. Elderly patients have more decreased vitamin D activation ability, less amount of food ingested, and are generally more affected by adverse effects due to chemotherapeutic agents than younger patients. With regard to ALP, Body et al. suggested that higher bone-specific ALP level at baseline is a risk factor for ≥grade 2 hypocalcemia. Approximately half of serum ALP has been reported to be derived from bone in healthy adults and indicates osteoblast specialization and bone formation. In addition, osteoblasts express RANKL, which is a target of denosumab, on the extracellular surface of osteoclasts; therefore, serum ALP could be a reasonable marker of hypocalcemia. A lower serum calcium level at baseline would be a considerable risk factor for all-grade hypocalcemia.

We should carefully observe the condition of the patients and consider an early evaluation of the serum calcium level and/or increase the supplementary dose in patients at risk for hypocalcemia.

Kidney dysfunction, such as CCr <30 mL/min, <50 mL/min, or 30 ≤ 60 mL/min, has been reported to be a risk factor for hypocalcemia; however, the first three reports did not evaluate ALP and not all patients were administered calcium/vitamin D supplementation in some studies. A relationship tends to exist between renal failure and the decreased serum calcium level; this is because the absorption of calcium is reduced due to the inactivation of vitamin D. Only two patients had CCr less than 30 mL/min at baseline. Further, these patients did not develop hypocalcemia, which could not be analyzed in the logistic analysis. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline suggested that a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² is associated with a higher risk of complications of chronic kidney disease (CKD) than in subjects with
CKD and conserved GFR. Therefore, we have set the cutoff of renal dysfunction as CCr 60 mL/min according to reports by Body et al. and the guideline. Accordingly, multivariate analysis suggested renal dysfunction was not a risk factor for all-grade hypocalcemia incidence in this study. Moreover, hypocalcemia incidence was 25.0 and 28.5% between patients with and without renal dysfunction at baseline, respectively, regardless of the higher rate of patients ≥65 years, which is a significant risk factor for hypocalcemia, among renal dysfunction patients (Supplementary Table 1). Furthermore, the incidence of hypocalcemia in patients with CCr <30 mL/min, 30 ≤60 mL/min, 60 ≤90 mL/min, and >90 mL/min was 0, 26.9, 31.6, and 23.5%, respectively. These results suggest that all-grade hypocalcemia similarly occur in patients with and without renal dysfunction under appropriate prescription control.

We evaluated the incidence of all-grade hypocalcemia. As shown in our previous report, its severity was milder than that in previous reports due to early intervention according to our management system, although the incidence rate was similar. In addition, there are some cases with a gradual decrease in serum calcium levels. It tends to appear in the early stages but also occurs after a certain period. We suppose that cases that occurred in the later phase appeared after a gradual decrease in the level, rather than hasty development. A patient with grade 2 hypocalcemia in this study also showed a gentle decrease, and finally reached the level after the fifth administration. Consequently, we consider that patients with grade 1 hypocalcemia under our system are at risk of degradation to grade 2 or higher, in cases without the system and/or longer administration. Therefore, it is meaningful to evaluate grade 1 patients in our facility.

This study had some limitations, which are similar to those of the previous report. This study was performed retrospectively, with a relatively small population of patients, and was limited to a single institution. A large, prospective, multicenter study is required to confirm these results. Second, all patients received denosumab for at least 6 months and with PS 0–1, suggesting that the patients were in relatively good condition. If we include the excluded patients with treatment <6 months, a shorter administration period can reduce the risk of hypocalcemia. Furthermore, the causes of denosumab discontinuation were progression of the disease and change.

| Table 2. Univariate and Multivariate Analyses of the Risk Factors Associated with the Incidence of Hypocalcemia |
|-------------------------------------------------|-----------------|-----------------|
| Hypocalcemia incidence (n, %)                  | Univariate analysis | Multivariate analysis |
|                                               | Odds ratio (95% CI) | p-Value | Odds ratio (95% CI) | p-Value |
| Sex                                            |                  |      |                    |      |
| Male                                           | 30 (32.3%)       |       | Excluded           | —     |
| Female                                         | 14 (21.5%)       |       |                    |      |
| Age (years)                                    |                  |      |                    |      |
| ≥65                                            | 31 (33.3%)       |       |                    |      |
| <65                                            | 13 (21.0%)       |       | 2.00 (0.95–4.21)   | 0.07  |
| Body weight (kg)                               |                  |      |                    |      |
| <60                                            | 27 (32.5%)       |       |                    |      |
| ≥60                                            | 22 (22.6%)       |       | 1.64 (0.81–3.34)   | 0.17  |
| Lung cancer                                    |                  |      |                    |      |
| Yes                                            | 18 (31.6%)       |       |                    |      |
| No                                             | 35 (26.1%)       |       | 1.70 (0.68–4.22)   | 0.26  |
| Prostate cancer                                |                  |      |                    |      |
| Yes                                            | 9 (37.5%)        |       |                    |      |
| No                                             | 35 (26.1%)       |       |                    |      |
| Creatinine clearance (mL/min)                  |                  |      |                    |      |
| ≤60                                            | 7 (25.0%)        |       |                    |      |
| >60                                            | 37 (28.5%)       |       | 0.84 (0.33–2.14)   | 0.71  |
| Liver dysfunction                              |                  |      |                    |      |
| Exist                                          | 11 (25.0%)       |       |                    |      |
| Absent                                         | 33 (29.9%)       |       |                    |      |
| Serum alkaline phosphatase ≥ grade 1 elevation | 27 (45%)         |       |                    |      |
| Normal                                         | 17 (17.3%)       |       | 3.90 (1.88–8.08)   | 0.03* |
| Serum albumin (g/dL)                           |                  |      |                    |      |
| ≤3.5                                           | 13 (38.2%)       |       |                    |      |
| >3.5                                           | 31 (25.0%)       |       | 1.86 (0.83–4.14)   | 0.13  |
| Adjusted serum calcium (mg/dL)                 |                  |      |                    |      |
| <9.3                                           | 13 (43.3%)       |       |                    |      |
| ≥9.3                                           | 31 (24.2%)       |       | 2.39 (1.05–5.47)   | 0.03* |
| Co-administration of corticosteroids           |                  |      |                    |      |
| Yes                                            | 6 (28.6%)        |       |                    |      |
| No                                             | 38 (27.7%)       |       | 1.04 (0.38–2.88)   | 0.94  |
| Co-administration of cytotoxic agents          |                  |      |                    |      |
| Yes                                            | 25 (37.3%)       |       |                    |      |
| No                                             | 19 (20.9%)       |       | 2.26 (1.11–4.58)   | 0.02* |

*: p < 0.05, **: p < 0.01. CI: confidence interval.
to the best supportive care (approximately 90%), switching to zoledronic acid, and osteonecrosis of the jaw (data not shown), suggesting that the patients' condition significantly changed during the period. Consequently, we excluded these patients, considering that evaluation including patients with shorter administration can affect the exact results. Further evaluation of patients with poor conditions will provide even more meaningful data. Third, the evaluation period was defined as 6 months. Therefore, the results in all treatment periods may be different. Fourth, we might have missed the lowest serum calcium level as some evaluation dates were 28d after the previous administration. Finally, other concomitant medicines might have affected the results, although we investigated co-administered drugs, such as calcitonin, cinacalcet hydrochloride, estrogen, oral bisphosphonates, raloxifene hydrochloride, vitamin K₂, and glucocorticoids by referring to a previous report.⁹

In conclusion, age ≥65 years, grade 1 or higher serum ALP elevation, adjusted serum calcium level <9.3 mg/dL at baseline, and co-administration of cytotoxic agents are risk factors for all-grade denosumab-induced hypocalcemia with calcium/vitamin D supplementation and consciousness in medical team care, as demonstrated in the management system of patients with bone metastasis. Our results advocate early detection of hypocalcemia incidence, to guide appropriate choice of management strategy. We will update our management system soon in response to these results.

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Conflict of Interest YS, YT, and MS have no conflict of interest. YK reports honoraria from Pfizer, Novartis, and Bayer, and research funding from Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult, and Taiho and provided speaking services for Eli Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer, and Taiho. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Supplementary Materials The online version of this article contains supplementary materials.

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