Pharmaceutical Intervention According to Strict Management System Can Normalize Decreased Serum Calcium Level by Denosumab and Prevent Its Aggravation

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Denosumab is a fully monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL), and prevents skeletal-related events by bone metastasis. Hypocalcemia is the most typical adverse effect of denosumab use. We have developed a management system for the more efficient and safer management of denosumab administration, and evaluated pharmaceutical interventions for the better control of hypocalcemia. All pharmaceutical interventions in the system from April 2016 to March 2020 were retrospectively evaluated. We have also assessed the incidence of hypocalcemia in 158 patients who were administered denosumab for six months or more in the period. A total of 282 pharmaceutical interventions (7.0% of the total administration) were conducted. The most conducted intervention was regarding hypocalcemia, which involved the suspension of the injection and/or the increase of calcium and vitamin D supplement with 65% adoption and 17% temporary treatment suspensions. Other interventions were about hypercalcemia, request of laboratory examination and ordering supplements, dental consultation, and poor renal function. A total of 199 interventions (70.6%) were adopted, with 33 administrations suspended. The frequency of hypocalcemia was 27.8% with just one patient having grade 2 hypocalcemia, suggesting that there were no severe cases. Moreover, hypocalcemia was significantly normalized following pharmaceutical intervention and/or handling by physicians (p = 0.02) according to the system. Conversely, the normalization rate in hypercalcemia did not differ according to the countermeasures. In conclusion, pharmaceutical interventions according to our management system benefit safe denosumab treatment, especially in severe hypocalcemia prevention.

Key words—denosumab; hypocalcemia; pharmaceutical management; calcium supplementation

INTRODUCTION

Bone metastasis is superimposed on malignancies such as breast (73%), prostate (68%), thyroid (42%), lung (36%) and kidney (35%). It disrupts the balance of osteogenesis and deossification by systemic factors released from the primary tumor and by local effectors released from tumor cells that have metastasized to bone. It significantly reduces the patients QOL. One of the most frequent symptoms is pain which is experienced by 60 to 70% of patients. Moreover, it is also associated with local irreversible skeletal-related events (SREs) such as pathologic fracture, spinal cord compression, severe pain, these all lead to significant decreases in their QOL.

Denosumab is a fully monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), which is the principal regulator of osteoclastic bone resorption. The main purposes of denosumab administration are preventing SREs occurrence and attenuating or avoiding the associated pain. The efficacy of denosumab is superior to zoledronic acid (which had been the mainstay of SRE prevention) and frequently administered to patients with bone metastasis. Conversely, hypocalcemia is the most typical adverse effect caused by denosumab. Some previous studies have reported that the incidence of hypocalcemia is more common in patients using denosumab than those on zoledronic acid. In Japan, after its approval in April 2012, it was administered to approximately 7300 patients in 4 months, resulting in 32 cases of serious hypocalcemia, including two deaths. Therefore, the Japanese Ministry of Health, Labour and Welfare stated that patients using denosumab should be administered oral calcium and vitamin D supplements, and that their serum calcium levels be monitored at frequent intervals, on September 2012.

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Delosumab and vitamin D supplement medicine (DENOTAS CHEWABLE COMBINATION TABLETS; Denotas), which contains precipitated calcium carbonate (762.5 mg), cholecalciferol (200 IU), and magnesium carbonate (59.2 mg) per tablet and is usually administered 2 tablets a day, was approved on May 2013.

It has also been reported that both denosumab and bisphosphonates induce osteonecrosis of the jaw (ONJ). It is recommended to consult a dentist for oral condition screening prior to administration, as well as regular dental checkups while using denosumab or bisphosphonates.8,9

At Hokkaido University Hospital, we developed a management system for the more efficient and safer management of denosumab administration for bone metastasis shortly after the statement (Fig. 1). In this study, we evaluated the associated pharmaceutical interventions and incidence of hypocalcemia.

PATIENTS AND METHODS

Patients and Interventions We retrospectively evaluated all pharmaceutical interventions regarding 120 mg denosumab administration from April 2016 to March 2020 in Hokkaido University Hospital; there were 405 patients who received 4070 doses.

Moreover, patients who were administered denosumab for six months or more in the period were assessed for the incidence, severity, time of appearance of hypocalcemia; there were 158 patients who received 948 doses (Fig. 2). Patients who were previously administered denosumab for osteoporosis and intravenous bisphosphonate, dosed it for giant cell tumor of bone, and whose administration interval of denosumab was more than five weeks were excluded.

The present study was approved by the Institutional Review Board of the Hokkaido University Hospital (approval number: 020-0096) and was carried out in
accordance with the Declaration of Helsinki. In view of the retrospective nature of the study, informed consent from the subjects was not mandated.

**Treatment Methods** Denosumab 120 mg was subcutaneously injected every four weeks as previously reported.\(^4,5\) All patients were administered Denotars, with the dose adjusted by the serum calcium level according to the system, after denosumab initiation.

**Practice According to the Management System**

The deadline of the denosumab order by a physician was defined as the morning prior to treatment. Pharmacists checked the denosumab prescription and laboratory data examination order by the day. On the day of administration, after the decision of the treatment was implemented by the physician, pharmacists checked the laboratory data and prescription again and discussed any problems with the physician. In the case of hypocalcemia, temporary treatment suspension was first proposed, and an increase in the dose of Denotars by one tablet and the early implementation of serum calcium evaluation were also suggested. In the case of hypercalcemia, a decrease in the dose of Denotars by one tablet was proposed. If the creatinine clearance (CCr) was less than 30 mL/min, treatment suspension, an increase in the dose of Denotars, and the early evaluation of serum calcium level were suggested. After confirmation, denosumab administration was performed.

**Evaluation of Patients and Serum Calcium Normalization** All the required information was obtained from medical records. Pharmaceutical intervention data was also extracted from the pharmacy ordering system (TOSHO®, Tokyo). Evaluation period of the incident, including severity, and time of appearance of hypocalcemia was defined to be six months from the initial denosumab administration. This period was selected as the first occurrence of grade 2 or more hypocalcemia has been shown to be after 3.8 (Q1–Q3, 1.8–10.1) months and that of grade 3 or more has been shown to be after 4.6 (Q1–Q3, 1.8–12.6) months.\(^6\) The daily living abilities of patients were assessed using Eastern Cooperative Oncology Group performance status (ECOG PS). CCr was assessed using the Cockcroft and Gault formula. We have calculated the serum calcium level using the Payne formula [Adjusted serum calcium level (mg/dL) = serum calcium level (mg/dL) − serum albumin (g/dL) + 4].\(^10\) The normal range of the adjusted serum calcium level was 8.8–10.1 mg/dL at our facility, and the severity of the hypocalcemia was graded in accordance with the Common Terminology Criteria for Adverse Events version 5.0. The normalization of the serum calcium level was compared between patients with and without the adoption of the intervention and those who did and who did not undergo countermeasures such as treatment suspension and/or Denotars dosage adjustment taken by the physicians and pharmacists in cases of hypocalcemia or hypercalcemia. We defined the normalization to be the preservation of a normal serum calcium level for 3 months after the intervention. In a previous report, serum calcium level has been reported to decrease the most after one denosumab administration.\(^11\) Thus, we considered that evaluation during three consecutive denosumab administration is suitable.

**Statistical Analysis** The normalization of serum calcium level following the intervention and countermeasures was evaluated using Fisher’s exact probability test. All analyses were conducted using JMP version 14.0 (SAS Institute Japan, Tokyo). Differences were considered to be statistically significant when \(p\)-values were less than 0.05.
RESULTS

Evaluation of Pharmaceutical Interventions

We have assessed pharmaceutical interventions according to the management system. A total of 4070 administrations in 405 patients were evaluated. A total of 282 pharmaceutical interventions were conducted (7.0% of the total administration). Details of the interventions are shown in Table 1. The most conducted intervention involved hypocalcemia, which suggested the temporary suspension of the injection and/or the increase of calcium and vitamin D supplements, and/or early serum calcium evaluation. Sixty five percent of the suggested interventions were adopted, and 17% resulted in temporary suspension of the treatment. The second most popular intervention involved hypercalcemia, which suggested a reduction in the supplement; this was adopted in approximately 60% of cases. The third and fourth most popular interventions involved the ordering of laboratory examination and calcium and vitamin D supplementation prescriptions; this intervention was accepted in approximately 90% of cases. Subsequently, interventions suggesting dental consultation (mostly screening for ONJ risk) were performed. Interventions due to poor renal function were conducted in 11 patients, and some countermeasures such as treatment suspension and early calcium examination were accepted in approximately half of the patients. Eventually, 199 interventions (70.6% of all interventions) were adopted, and a total of 33 administrations, which suggests that approximately one treatment per month, was suspended by pharmaceutical intervention.

Evaluation of Incidence and Severity of Hypocalcemia

Patient characteristics The baseline characteristics of patients with an administration period of six months or more are shown in Table 2. A total of 158 patients were evaluated. All patients were assessed for...
Variation of serum calcium level (median, range, IQR)

| Variation of serum calcium level | Baseline | Lowest | Variation |
|---------------------------------|----------|--------|-----------|
|  | 9.5 (8.8–11.2, 9.3–9.8) | 9.0 (7.0–9.9, 8.7–9.2) | −0.6 (−2.4–0.3, −0.9–0.3) |

Administration time to the lowest level (median, range, IQR)

| Incidence of hypocalcemia | 44 |
| Administration time to hypocalcemia (median, range, IQR) | 2 (1–6, 1–3) |

Patients experienced denosumab suspension due to hypocalcemia 13

IQR, interquartile range.

Table 4. Normalization Rate of Serum Calcium Level following the (A) Pharmaceutical Intervention and (B) Total Countermeasures Taken by Physicians and Pharmacists

(A)

| Patients with intervention | Normalization rate (%) | p-value |
|----------------------------|------------------------|---------|
|                            | With adoption | Without adoption |       |
| Hypocalcemia (n = 21)      | 85.7% (12) | 28.6% (2) | 0.02* |
| Hypercalcemia (n = 16)     | 92.6% (13) | 50.0% (1) | 0.24  |

*B < 0.05.

(B)

|                      | Normalization rate (%) | p-value |
|----------------------|------------------------|---------|
|                      | With countermeasure | Without countermeasure |       |
| Hypocalcemia (n = 44) | 83.3% (30) | 37.5% (3) | 0.02* |
| Hypercalcemia (n = 23) | 85.7% (18) | 50.0% (1) | 0.32  |

*B < 0.05.

PS 0–1, patients with liver dysfunction (grade 1 or higher aspartate aminotransferase, alanine aminotransferase, or total bilirubin elevation) totaled 27.8%, patients whose Ccr were less than 60 mL/min totaled 17.7%. All patients had a baseline of a normal adjusted serum calcium level.

Variation of serum calcium level and incidence of hypocalcemia

Variation of the serum calcium level and incidence of hypocalcemia are shown in Table 3. The median variation in the serum calcium level was 0.6 mg/dL lower than the baseline, appearing after the second administration. The incidence of hypocalcemia was 27.8%, this included just one patient in grade 2. The median time of the initial hypocalcemia incidence was after the second administration as well as within the lowest serum calcium level. Approximately 8% of patients experienced treatment suspension.

Comparison of serum calcium normalization rate

Serum calcium normalization was confirmed in 85.7% of patients with intervention adoption, which was significantly higher than that in patients without intervention adoption (28.6%, p = 0.02) in hypocalcemia [Table 4(A)]. In addition, the rate of total countermeasures taken by physicians and pharmacists was 83.3% and that in follow-up patients was 37.5% with hypocalcemia, which was significantly improved by the countermeasure (p = 0.02) [Table 4(B)]. However, the normalization rate of hypercalcemia was not statistically different between patients with and without intervention adoption (p = 0.24), and this result was also confirmed between patients in whom countermeasures were taken and those in whom they were not taken (p = 0.32).
DISCUSSION

Denosumab is the preferred medicine for bone metastasis treatment, unfortunately, hypocalcemia occurs in 5–50% of patients.11-13 Moreover, it has also been reported to occur in approximately 30% of patients with advanced prostate cancer.14,15 We have developed a management system for the more efficient and safer denosumab administration, focused on hypocalcemia and ONJ, and evaluated pharmaceutical interventions and the incidence of hypocalcemia for better management in the future.

In our evaluation of the interventions, approximately 20% of the interventions due to hypocalcemia resulted in temporary treatment suspension. In addition, some sort of measure such as a dose adjustment of calcium and vitamin D supplementation and/or front-loaded calcium examination was performed in approximately half of the interventions. A previous report suggested that the median time of the initial occurrence of hypocalcemia is 3.8 months (Q1–Q3, 1.8–10.1 months).6 Another study reported that the number of injections before the occurrence of hypocalcemia is one (median value, mean 2.8), ranging from 1 to 14.11 Moreover, the serum calcium level significantly decreases 3 days after denosumab administration and the median degradation level after 1 week is 1.4 mg/dL, and that after 2 weeks is 1.7 mg/dL.16,17 Therefore, we should be aware of the potential for hypocalcemia and monitoring for variations in the serum calcium level for early detection.

The increase in Denotas dosage by the intervention resulted in a significantly greater serum calcium normalization than that without the intervention adoption in patients with hypocalcemia. Moreover, not only pharmacists but also physicians had taken countermeasures such as treatment suspension and/or dose change of supplementation according to the system. Therefore, we also evaluated the normalization of calcium levels following total countermeasures taken by physicians and pharmacists. The normalization rates in hypocalcemia and hypercalcemia were similar to those of the pharmaceutical intervention. From these results, countermeasures including the pharmaceutical interventions according to the management system were suggested to be effective for preventing hypocalcemia degradation. Other interventions due to prescription errors such as leakage or a shortage of calcium and vitamin D supplementation, especially 6% of leakage in the first administration (data not shown), laboratory examination omission, and renal dysfunction, which may be associated with hypocalcemia, were also conducted according to the system.

The incidence of any grade of hypocalcemia was 27.8%, with just one patient (0.6%) with grade 2. The incidence of grade 2 or higher hypocalcemia in this study seems to be lower than that in previous reports (7.7–17.3%) even though the patients’ background and treatment duration are different.6,11,17,18 Moreover, the median variation in serum calcium level was 0.6 mg/dL lower than that at the baseline, which suggests that the probability of severe hypocalcemia is low with appropriate administration. Temporary treatment suspension, increased calcium/vitamin D supplementation, and front-loaded calcium examination according to the system contributed to the results. This initial report suggests that strict pharmaceutical management is beneficial for safe denosumab administration as it reduces the severity of hypocalcemia, with no severe cases observed in this study.

However, the adoption rate of this intervention was 70.6%, which was similar to our previous report on outpatient chemotherapy.19 Pharmaceutical interventions such as prescription questions confirm prescription errors and suggest proposals for better methods, respectively. We sometimes check problems again even if physicians have already taken measures, depending on the patient’s situation. In hypocalcemia, the proposed interventions were not implemented because the physicians considered the possibility of severe hypocalcemia to be low, as the variation in serum calcium level was small (50%), the patients did not always take Denotas for various reasons and took other measures instead (20.8%); moreover, the physicians had already planned an early evaluation (20.8%). Considering the possibility of hypercalcemia, the physicians determined that not implementing the proposed interventions would pose few problems as the variation was small (36.4%), the level would decrease by denosumab administration (31.8%), it was one point elevation (18.2%), and the physicians had already planned an early evaluation (13.6%). As the normalization rate was not statistically different regardless of whether the intervention was adopted in patients with hypercalcemia, we should assess how to discriminate significant hypercalcemia from nonsig-
significant hypercalcemia. However, as some interventions without adoption resulted in early countermeasures by physicians, they are meaningful and essential in practice.

It has been reported that 1.8% of denosumab-administered patients develop ONJ although its common time of appearance is unknown. Dental screening prior to denosumab administration in isolation is insufficient, regular oral care is necessary for the early detection of ONJ. In contrast, the duration of a dental visit is often longer than that of denosumab administration, and some patients resist frequent visits to the hospital. Therefore, general questions to make an informed dental assessment by other medical staff are helpful when denosumab is administered. Our management system provides an early detection system for dental issues, and the growing concern for dental care in medical staff.

The literatures show that oncology pharmacists contribute to the safe management of adverse drug reactions by chemotherapeutic agents. In addition, the construction of an agreement such as collaborative drug therapy management (CDTM) has been proved effective in the management of cancer patients. It is more suitable to create agreements within the medical team rather than depend on any individual’s ability to ensure continuity in the quality of the clinical practice and educate junior pharmacists. This management system provides a good model for quality management of denosumab administration that encompasses various professional requirements.

There are some limitations when evaluating our effort in denosumab treatment. First, this study was retrospective, conducted at a single institution without a control group, and used a relatively small population of patients, especially to determine the normalization rate. We attempted to evaluate the efficacy of our system by comparison between before and after the system induction. However, few patients before the system induction met the criteria as the duration without the management system was only 6 months, and Denotas was approved after the induction. Therefore, we decided to conduct a single-arm study. It is necessary to conduct a comparative study with institutions without this management system. Second, all patients evaluated about hypocalcemia continued its administration for at least 6 months and with PS 0–1, suggesting the patients were in relatively good condition. Future research should involve also assessing patients with poor condition. Third, it has been reported that approximately 40% of patients experience their first incidence of hypocalcemia 6 months after the initial denosumab administration. Assessment in the longer term may reveal other outcomes. Finally, some evaluation dates were 28 days after previous administration; therefore, we might not have assessed the lowest serum calcium level.

In conclusion, we have demonstrated that pharmaceutical management according to the management system is effective for safe denosumab administration, as it can normalize the serum calcium level and attenuate the severity of hypocalcemia. The results obtained in this study will inspire more appropriate standardized pharmacy practices.

Authors’ Contributions YS, KU, and TS participated in research design. YS conducted experiments. YS, KU, and TS performed data analysis. All authors wrote or contributed to the writing of the manuscript.

Conflict of Interest YS, KU, TS, KY, KK, YT, 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 speaker services for Eli Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer and Taiho.

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