

Development of a Practice Standard for Monitoring Adult Patients Receiving Bone-Modifying Agents at a Community Cancer Center

ANTON NGUYEN,¹ PharmD, JOSEPH A. KALIS,² PharmD, BCOP, THERESA R. SUTZ,¹ PharmD, and KATE D. JEFFERS,² PharmD, BCOP

From ¹Pharmacy Department, University of Colorado Health Memorial Hospital, Colorado Springs, Colorado; ²Cancer Care and Hematology, University of Colorado Health Memorial Hospital, Colorado Springs, Colorado

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Anton Nguyen, PharmD, 170 N. 1100 E., American Fork, UT 84003.
E-mail: slc.anton.n@gmail.com

<https://doi.org/10.6004/jadpro.2018.9.6.3>

© 2018 Harborside™

Abstract

The purpose of this study is to develop a standard for monitoring outpatients starting bone-modifying agents (BMAs) at a community cancer center. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend the monitoring of serum magnesium and phosphorus during BMA therapy but do not define a standard interval. The risk of hypomagnesemia and hypophosphatemia was assessed for the BMAs denosumab, pamidronate, and zoledronic acid. Compliance with dental clearance was also evaluated. Adult cancer outpatients newly started on BMAs between January 1, 2016, to December 31, 2016, were evaluated. Patients with hypercalcemia of malignancy were excluded. Primary endpoints were the composite rates of grade 3 and 4 hypomagnesemia and hypophosphatemia. Secondary endpoints included all-grade hypomagnesemia, all-grade hypophosphatemia, charges for laboratory draws, rate of dental clearance, and rate of osteonecrosis of the jaw (ONJ). Among 61 patients, 4.3% experienced grade 3 and 4 hypophosphatemia. No cases of grade 3 and 4 hypomagnesemia occurred. The annual cost for serum magnesium and phosphorus lab draws totaled \$9,144.80. Dental clearance was obtained in 100% of patients, with 67% of clearances obtained from a dentist. No patients developed ONJ. Composite rates of grade 3 and 4 hypomagnesemia and hypophosphatemia were lower than reported in the literature. We propose to monitor magnesium and phosphorus levels at baseline, and then every 6 months. More frequent laboratory draws may be indicated based on clinical judgment. This recommendation will reduce laboratory draws and provide cost savings for patients. Compliance with dental clearance was fully achieved.

Bone health is a critical aspect of cancer management, as bone complications can significantly reduce patients' quality of life and survival (Hernandez et al., 2015). Cancer treatments such as hormonal therapy, chemotherapy, glucocorticoids, and radiation can decrease bone mineral density (Guise, 2006). Additionally, bone complications often occur as a result of metastases and multiple myeloma. Significant morbidity and skeletal-related events (SREs) can occur, including pathologic fractures, spinal cord compression, severe pain, impaired mobility, and declining performance status. Risk factors for SREs include endocrine therapy, low bone mineral density (T-score of -1 or lower on a bone mineral density test), older age, chronic corticosteroid use, low body mass index (body mass index less than 18.5 kg/m²), prior history of fracture, family history of fracture, smoking, excessive alcohol intake, inadequate weight-bearing exercise, low calcium intake, and vitamin D deficiency (Centers for Disease Control and Prevention, 2016; Gralow et al., 2013; National Institutes of Health Osteoporosis and Related Bone Diseases National Resource Center, 2015).

Effective prevention and treatment of bone loss can delay complications, relieve symptoms, and improve patients' quality of life. Injectable pharmacologic options, known as bone-modifying agents (BMAs), include denosumab (Prolia, Xgeva), pamidronate (Aredia), and zoledronic acid (Reclast, Zometa). Pamidronate and zoledronic acid are bisphosphonates, which inhibit bone resorption and decrease mineralization by disrupting osteoclast activity (Ben Venue Laboratories, Inc., 1991; Novartis Pharmaceutical Corporation, 2001). Denosumab is a monoclonal antibody to receptor activator of nuclear factor κ B ligand (RANKL). It inhibits osteoclast differentiation, proliferation, and function (Amgen, Inc., 2010). The risks of

BMAs include acute-phase response, hypocalcemia, atypical femur fracture, nephrotoxicity with bisphosphonates, hypomagnesemia, hypophosphatemia, and osteonecrosis of the jaw (ONJ).

Osteonecrosis of the jaw is a rare, serious side effect of BMA use (Gralow et al., 2013). Risk factors include increasing duration of BMA use, dental extractions, invasive procedures, periodontitis, and poor oral hygiene. Signs and symptoms involve tooth pain, jaw pain, feeling of loose teeth, swelling of the jaw, ongoing and recurrent dental infections, and exposure of jaw bone on physical examination. The American Association of Oral and Maxillofacial Surgeons and the US Food and Drug Administration labeling recommends all patients with cancer receive a dental examination and necessary preventive dental care prior to starting BMA therapy, unless factors exist which preclude dental assessment (Ruggiero et al., 2014). Our institution requests dental clearance prior to the initiation of BMAs.

The National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines recommend regular monitoring of serum magnesium and phosphorus during BMA therapy but do not specify a standard interval (Gralow et al., 2013; Van Poznak et al., 2011). At our community cancer center, serum magnesium and phosphorus labs are built into treatment plans for each injectable BMA. These labs are routinely monitored with each treatment cycle. Grade severity is based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Definitions can be found in Table 1 (National Institutes of Health, 2009). The reported incidences from the literature of grade 3 and 4 hypomagnesemia and hypophosphatemia for each BMA can be found in Table 2 (Amgen, Inc., 2010; Ben Venue Laboratories, Inc., 1991; Novartis Pharmaceutical Corpora-

Table 1. Definitions of Grade 3 and 4 Hypomagnesemia and Hypophosphatemia Based on CTCAE Version 4.0

Reported risk	CTCAE definition
Grade 3 hypomagnesemia	< 0.9-0.7 mg/dL
Grade 4 hypomagnesemia	< 0.7 mg/dL
Grade 3 hypophosphatemia	< 2.0-1.0 mg/dL
Grade 4 hypophosphatemia	< 1.0 mg/dL

Note. CTCAE = Common Terminology Criteria for Adverse Events. Information from National Institutes of Health (2009).

Table 2. Reported Incidences of Grade 3 and 4 Hypomagnesemia and Hypophosphatemia for Each Injectable Bone-Modifying Agent From the Literature

Reported risk	Denosumab	Pamidronate	Zoledronic acid
Grade 3 hypomagnesemia (%)	0	0	< 1
Grade 4 hypomagnesemia (%)	0	< 1	< 1
Grade 3 hypophosphatemia (%)		7	12
Grade 4 hypophosphatemia (%)	15.4 ^a	0	< 1

Note. Information from Amgen, Inc. (2010); Ben Venue Laboratories, Inc. (1991); Novartis Pharmaceutical Corporation (2001).
^aCombined incidence of grade 3 and 4 hypophosphatemia.

tion, 2001). No evidence is currently available to guide the interval for monitoring serum magnesium and phosphorus with BMAs.

The purpose of this study is to develop a standard for monitoring serum magnesium and phosphorus in adult outpatients newly initiated on denosumab, pamidronate, and zoledronic acid at a community cancer center. Patients' laboratory charges for serum magnesium and phosphorus were tracked. Compliance with dental clearance and incidence of ONJ were also evaluated.

METHODS

A retrospective, descriptive study was conducted from January 1, 2016, to December 31, 2016, at a community cancer center. The study was reviewed and approved by the institutional review board. Patient data were collected from electronic chart reviews.

Patient demographics collected included age, sex, use of active chemotherapy at baseline, presence of bone metastases at baseline, height, weight, serum creatinine, creatinine clearance based on the Cockcroft-Gault equation, chronic kidney disease diagnosis, oncologic diagnoses, and number of BMA cycles received. Inclusion criteria were cancer outpatients 18 years of age or older newly initiated on denosumab, pamidronate, or zoledronic acid. Figure 1 illustrates patients screened and included. Patients were excluded for the following reasons: treatment of hypercalcemia of malignancy (HCM), treatment use prior to the study period, or treatment administered at another institution.

The primary endpoints are composite rates of grade 3 and 4 hypomagnesemia and grade 3 and 4 hypophosphatemia. Secondary endpoints include rate of all-grade hypomagnesemia, rate of

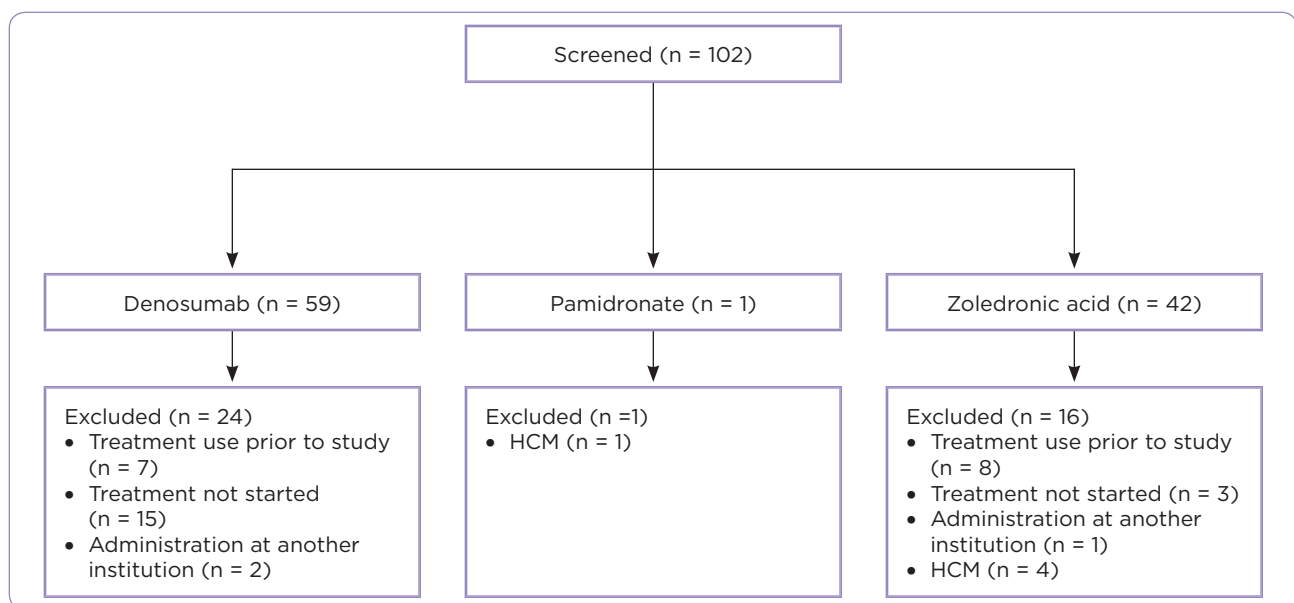


Figure 1. Screening, inclusion, and exclusion of patients by treatment group. HCM = hypercalcemia of malignancy.

all-grade hypophosphatemia, patient charge for serum magnesium and phosphorus levels, proportion of cycles with serum magnesium and phosphorus draws, dental clearance rate by a dentist, and ONJ incidence. Descriptive statistics were used to describe patient characteristics.

RESULTS

Baseline patient characteristics are reported in Table 3. A total of 61 patients were included for final analysis. One patient on pamidronate was screened but then excluded due to BMA use for HCM. Eighteen patients were excluded for treatment not being started pending insurance authorization and/or dental clearance. Patients' ages ranged between 32 to 85 years of age. The median age was 67, with the majority of the population being female. A higher rate of patients were receiving concomitant active chemotherapy at baseline in the zoledronic acid group compared to the denosumab group. Similarly, there was a higher rate of bone metastases in the zoledronic acid group. Most patients had normal renal function based on creatinine clearance calculations. Seventy-two percent of patients received hormonal cancer therapy at baseline. Table 4 shows rates of oncologic diagnoses. The most frequently encountered oncologic diagnosis was breast cancer followed by lung cancer. One patient was diagnosed with both multiple myeloma and breast cancer.

Table 5 illustrates primary and secondary outcomes related to hypomagnesemia and hypophosphatemia. Magnesium and phosphorus levels were drawn 115 times each for the entire study population with approximately half of lev-

els drawn for each group. There were no cases of grade 3 and 4 hypomagnesemia. Compared to the zoledronic acid group, the denosumab group had a slightly higher rate of composite grade 3 and 4 hypophosphatemia (5% vs. 3.6%, respectively). The denosumab group also had slightly higher rates of all-grade hypomagnesemia (6.7% vs. 5.5%) and all-grade hypophosphatemia (13.3% vs. 10.9%) compared to the zoledronic acid group.

Table 6 shows BMA cycles with laboratory draws and annualized patient charge for levels. Approximately 79% of all treatment cycles included serum magnesium and phosphorus laboratory draws. There was a higher rate of cycles with laboratory draws in the denosumab group compared to the zoledronic acid group (89.6% vs. 70.5%). At the study site, patient charge per serum magnesium level was \$46.29 and patient charge per serum phosphorus level was \$33.23. The annual patient charge for serum magnesium and phosphorus laboratory draws was slightly greater in the denosumab group since this group had 5 more cycles with draws compared to the zoledronic acid group.

Table 7 shows dental clearance by a dentist and incidence of ONJ. Rates of dental clearance by a dentist were similar between both treatment groups with a total rate of 67.2% for all patients. Compliance with dental clearance was achieved in 100% of patients based on oncologist documentation and dentist letters. No patients were diagnosed with ONJ over the 1-year period.

DISCUSSION

Study limitations are a small sample size, single-center study, descriptive design, and short study dura-

Table 3. Baseline Patient Characteristics

Characteristic	Denosumab (n = 35)	Zoledronic acid (n = 26)	Total (n = 61)
Age, years, median (IQR)	66 (61-73.5)	67.5 (59.3-72.5)	67 (61-73)
Female, n (%)	26 (74.3)	20 (76.9)	46 (75.4)
Concomitant active chemotherapy at baseline, n (%)	12 (34.3)	11 (42.3)	23 (37.7)
Bone metastases at baseline, n (%)	12 (34.3)	11 (42.3)	23 (37.7)
Serum creatinine, mg/dL, median (IQR)	0.82 (0.74-0.95)	0.81 (0.65-0.90)	0.82 (0.72-0.94)
Creatinine clearance, mL/min, median (IQR)	62.2 (41.4-76.4)	55.4 (51.5-76.5)	60.1 (50.1-77.1)
Chronic kidney disease, n (%)	2 (5.7)	1 (3.8)	3 (4.9)

Note. IQR = interquartile range.

Table 4. Cancer Diagnoses

Oncologic diagnosis	Denosumab (n = 35)	Zoledronic acid ^a (n = 27)	Total (n = 62)
Breast cancer, n (%)	25 (71.4)	15 (55.6)	40 (64.5)
Lung cancer, n (%)	4 (11.4)	5 (18.5)	9 (14.5)
Prostate cancer, n (%)	3 (8.6)	3 (11.1)	6 (9.7)
Multiple myeloma, n (%)	0 (0)	3 (11.1)	3 (4.8)
Colon cancer, n (%)	1 (2.9)	0 (0)	1 (1.6)
Esophageal cancer, n (%)	1 (2.9)	0 (0)	1 (1.6)
Squamous cell carcinoma, n (%)	0 (0)	1 (3.7)	1 (1.6)
Giant cell tumor of bone, n (%)	1 (2.9)	0 (0)	1 (1.6)

Note. ^aOne patient was diagnosed with two different cancers.

tion. Most patients are treated for longer than 1 year or indefinitely, which underestimates actual cost savings. In addition, ONJ has a mean onset of 1 to 3 years after initiating an injectable BMA (Rasmusson & Abtahi, 2014). No patients on pamidronate were included in the study. Data was unavailable for patients treated at another institution, although they were followed by the oncologists at the study site.

Study strengths are exclusion of patients treated for HCM, use of CTCAE version 4.0, and evaluation of patients newly initiated on BMAs. Hypercalcemia of malignancy is an oncologic emergency and precludes dental clearance. It may also overestimate the incidence of hypophosphatemia. CTCAE version 4.0 provides severity grades with grade 3 indicating the need for hospitalization and grade 4 indicating a life-threatening risk (National Institutes of Health, 2009). Evaluation of new starts allows for better validation of risks.

Composite rates of grade 3 and 4 hypomagnesemia and hypophosphatemia in the study were lower than the rates reported in the package inserts (Amgen, Inc., 2010; Novartis Pharmaceutical Corporation, 2001). These low incidences support a change in the monitoring interval of magnesium

and phosphorus levels at our cancer center, where these levels are routinely monitored with each BMA cycle. For this 1-year study, the approximate number of BMA doses administered per patient was 2 cycles. The billed charge for 2 cycles of serum magnesium and phosphorus laboratory draws was \$159.04.

Despite our current practice of drawing magnesium and phosphorus levels with each cycle, laboratory orders were not drawn in approximately 20% of the cycles. Magnesium and phosphorus labs were not released from the treatment orders in these cases, and no explanation was provided in the documentation. There was a greater proportion of cycles with serum magnesium and phosphorus draws in the denosumab group, indicating greater provider awareness for risk of hypomagnesemia and hypophosphatemia associated with the use of this medication. The annual charge for drawing both levels totaled \$9,144.80 in the study. If levels were drawn for every cycle based on our current practice, the annual cost would be approximately \$11,500.

Based upon our findings, we recommend the following: Serum magnesium and phosphorus

Table 5. Primary and Secondary Outcomes Related to Hypomagnesemia and Hypophosphatemia

Outcome	Denosumab (n = 60)	Zoledronic acid (n = 55)	Total (n = 115)
Composite grade 3 and 4 hypomagnesemia, n (%)	0 (0)	0 (0)	0 (0)
Composite grade 3 and 4 hypophosphatemia, n (%)	3 (5)	2 (3.6)	5 (4.3)
All-grade hypomagnesemia, n (%)	4 (6.7)	3 (5.5)	7 (6.1)
All-grade hypophosphatemia, n (%)	8 (13.3)	6 (10.9)	14 (12.2)

Table 6. Bone-Modifying Agent Cycles and Patients' Charges for Magnesium and Phosphorus Levels

	Denosumab	Zoledronic acid	Total
Outcome			
Cycles with serum magnesium and phosphorus lab draws, number/total number (%)	60/67 (89.6)	55/78 (70.5)	115/145 (79.3)
Annual cost analysis			
Patients' charge for serum magnesium lab draws	\$2,777.40	\$2,545.95	\$5,323.35
Patients' charge for serum phosphorus lab draws	\$1,993.80	\$1,827.65	\$3,821.45
Patients' charge for serum magnesium and phosphorus lab draws	\$4,771.20	\$4,373.60	\$9,144.80

levels should be drawn at baseline and then every 6 months for cancer outpatients on injectable BMAs. Clinical judgment should be used if more frequent laboratory draws are needed, such as in patients with renal insufficiency, symptoms suggestive of hypomagnesemia and hypophosphatemia, and baseline hypomagnesemia and hypophosphatemia. The proposed change will lead to cost savings and reduce the amount of serum magnesium and phosphorus draws.

CONCLUSION

Composite rates of grade 3 and 4 hypomagnesemia and hypophosphatemia were lower than the rates reported in the literature for denosumab and zoledronic acid. No patients on pamidronate were included in the data analysis. Based on the low incidences of grade 3 and 4 hypomagnesemia and hypophosphatemia in both the literature and this study, we propose to monitor serum magnesium and phosphorus levels at baseline, and then every 6 months. More frequent draws may be considered based on clinical judgment. Dental clearance was obtained in all patients, with dental letters acquired for 67% of patients. No cases of ONJ were reported. ●

Disclosure

Dr. Jeffers has served on advisory boards for Take-

da Oncology, Tesaro, and Oncology Reimbursement Management, and served on the speakers bureau for Amgen.

References

- Amgen, Inc. (2010). Xgeva (denosumab) package insert. Retrieved from http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf
- Ben Venue Laboratories, Inc. (1991). Pamidronate package insert.
- Centers for Disease Control and Prevention. (2016). Defining adult overweight and obesity. Retrieved from <https://www.cdc.gov/obesity/adult/defining.html>
- Gralow, J. R., Biermann, J. S., Farooki, A., Fornier, M. N., Gage, R. F., Kumar, R.,...Van Poznak, C. H. (2013). NCCN Task Force Report: Bone health in cancer care. *Journal of the National Comprehensive Cancer Network*, 11, S1-S50. <https://doi.org/10.6004/jnccn.2013.0215>
- Guise, T. A. (2006). Bone loss and fracture risk associated with cancer therapy. *Oncologist*, 11(10), 1121-1131. <https://doi.org/10.1634/theoncologist.11-10-1121>
- Hernandez, R. K., Adhia, A., Wade, S. W., O'Connor, E., Arellano, J., Francis, K.,...Liede, A. (2015). Prevalence of bone metastases and bone-targeting agent use among solid tumor patients in the United States. *Clinical Epidemiology*, 2015(7), 335-345. <https://doi.org/10.2147/CLEP.S85496>
- National Institutes of Health. (2009). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Retrieved from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
- National Institutes of Health Osteoporosis and Related Bone Diseases National Resource Center. (2015). Bone mass measurement: What the numbers mean (NIH Publication No. 15-7877-E). Retrieved from <https://www.bones.nih.gov/health-info/bone/bone-health/bone-mass-measurement-what-numbers-mean>

Table 7. Dental Clearance by a Dentist and Incidence of Osteonecrosis of the Jaw

	Denosumab (n = 35)	Zoledronic acid (n = 26)	Total (n = 61)
Outcome			
Dental clearance by a dentist, n (%)	24 (68.6)	17 (65.4)	41 (67.2)
ONJ, n (%)	0 (0)	0 (0)	0 (0)

Note. ONJ = osteonecrosis of the jaw.

- Novartis Pharmaceutical Corporation. (2001). Reclast (zoledronic acid) package insert. Retrieved from <http://www.pharma.us.novartis.com/product/pi/pdf/reclast.pdf>
- Rasmusson, L., & Abtahi, J. (2014). Bisphosphonate associated osteonecrosis of the jaw: An update on pathophysiology, risk factors, and treatment. *International Journal of Dentistry*, 2014, Article ID 471035. <https://doi.org/10.1155/2014/471035>
- Ruggiero, S. L., Dodson, T. B., Fantasia, J., Goodday, R., Aghaloo, T., Mehrotra, B.,...O’Ryan, F. (2014). American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *Journal of Oral and Maxillofacial Surgery*, 72(10), 1938–1956. <https://doi.org/10.1016/j.joms.2014.04.031>
- Van Poznak, C. H., Temin, S., Yee, G. C., Janjan, N. A., Barlow, W. E., Biermann, J. S.,...Von Roenn, J. H. (2011). American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *Journal of Clinical Oncology*, 29(9), 1221–1227. <https://doi.org/10.1200/JCO.2010.32.5209>