

# Skeletal-Related Events in Patients With Multiple Myeloma and Prostate Cancer Who Receive Standard vs Extended-Interval Bisphosphonate Dosing

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In patients with multiple myeloma and prostate cancer, extending the bisphosphonate dosing interval may help decrease medication-related morbidity without compromising therapeutic benefit.

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**B**one pain is one of the most common causes of morbidity in multiple myeloma (MM) and metastatic prostate cancer (CaP). This pain originates with the underlying pathologic processes of the cancer and with downstream skeletal-related events (SREs). SREs—fractures, spinal cord compression, and irradiation or surgery performed in  $\geq 1$  bone sites—represent a significant health care burden, particularly given the incidence of the underlying malignancies. According to American Cancer Society statistics, CaP is the second most common cancer in American men, and MM the second most common hematologic malignancy, despite its relatively low overall lifetime risk.<sup>1,2</sup> Regardless of the underlying malignancy, bisphosphonates are the cornerstone of SRE prevention, though the optimal dosing strategy is the subject of clinical debate.

Although similar in SRE incidence, MM and CaP have distinct pathophysiologic processes in the dysregulation of bone resorption. MM is a hematologic malignancy that increases the risk of SREs by osteoclast up-regulation, primarily through the RANK (receptor activator of nuclear factor  $\alpha$ -B) signaling pathway.<sup>3</sup> CaP is a solid tumor malignancy that metastasizes to bone. Dysregulation of the bone resorption or formation cycle and net bone loss are a result of endogenous osteoclast up-regulation in response to abnormal bone formation in osteoblastic bone metastases.<sup>4</sup> Androgen-deprivation therapy, the cornerstone of CaP treatment, further predisposes CaP patients to osteoporosis and SREs.

Prevention of SREs is pharmacologically

driven by bisphosphonates, which have anti-resorptive effects on bone through promotion of osteoclast apoptosis.<sup>5</sup> Two IV formulations, pamidronate and zoledronic acid (ZA), are US Food and Drug Administration approved for use in bone metastases from MM or solid tumors.<sup>6-10</sup> Although generally well tolerated, bisphosphonates can cause osteonecrosis of the jaw (ONJ), an avascular death of bone tissue, particularly with prolonged use.<sup>11</sup> With its documented incidence of 5% to 6.7% in bone metastasis, ONJ represents a significant morbidity risk in patients with MM and CaP who are treated with IV bisphosphonates.<sup>12</sup>

Investigators are exploring bisphosphonate dosing intervals to determine which is most appropriate in mitigating the risk of ONJ. Before 2006, bisphosphonates were consistently dosed once monthly in patients with MM or metastatic bone disease—a standard derived empirically rather than from comparative studies or compelling pharmacodynamic data.<sup>13-15</sup> In a 2006 consensus statement, the Mayo Clinic issued an expert opinion recommendation for increasing the bisphosphonate dosing interval to every 3 months in patients with MM.<sup>16</sup> The first objective evidence for the clinical applicability of extending the ZA dosing interval was reported by Himmelstein and colleagues in 2017.<sup>17</sup> The randomized clinical trial found no differences in SRE rates when ZA was dosed every 12 weeks,<sup>17</sup> prompting a conditional recommendation for dosing interval extension in the American Society of Clinical Oncology MM treatment guidelines (2018).<sup>13</sup> Because of the age and racial demographics of the pa-

tients in these studies, many questions remain unanswered.

For the US Department of Veterans Affairs (VA) population, the pharmacokinetic and dynamic differences imposed by age and race limit the applicability of the available data. However, in veterans with MM or CaP, extending the bisphosphonate dosing interval may help decrease medication-related morbidity (eg, ONJ, nephrotoxicity) without compromising therapeutic benefit. To this end at the Memphis VA Medical Center (VAMC), we assessed for differences in SRE rates by comparing outcomes of patients who received ZA in standard- vs extended-interval dosing.

## METHODS

We retrospectively reviewed the Computerized Patient Record System for veterans with MM or metastatic CaP treated with ZA at the Memphis VAMC. Study inclusion criteria were aged > 18 years and care provided by a Memphis VAMC oncologist between January 2003 and January 2018. The study was approved by the Memphis VAMC's Institutional Review Board, and procedures were followed in accordance with the ethical standards of its committee on human experimentation.

Using Microsoft SQL 2016 (Redmond, WA), we performed a query to identify patients who were prescribed ZA during the study period. Exclusion criteria were ZA prescribed for an indication other than MM or CaP (ie, osteoporosis) and receipt of ≤ 1 dose of ZA. Once a list was compiled, patients were stratified by ZA dosing interval: standard (mean, every month) or extended (mean, every 3 months). Patients whose ZA dosing interval was changed during treatment were included as independent data points in each group.

Skeletal-related events included fractures, spinal compression, irradiation, and surgery. Fractures and spinal compression were pertinent in the presence of radiographic documentation (eg, X-ray, magnetic resonance imaging scan) during the period the patient received ZA or within 1 dosing interval of the last recorded ZA dose. Irradiation was defined as documented application of radiation therapy to ≥ 1 bone sites for palliation of pain or as an intervention in the setting of spinal compression. Surgery was defined as any procedure

**TABLE 1**  
**Baseline Patient Characteristics**

Variables	Zoledronic Acid Interval Dosing	
	Standard (n = 121)	Extended (n = 35)
Age, mean (SD), y	69 (10)	68 (10)
Race, No. (%)		
White	45 (37)	10 (29)
African American	75 (62)	25 (71)
Other	1 (1)	0 (0)
Sex, No. (%)		
Male	118 (98)	34 (97)
Female	3 (2)	1 (3)
Malignancy, No. (%)		
Multiple myeloma	21 (7)	7 (20)
Prostate cancer	100 (83)	28 (80)
Dental screening, No. (%)		
Before	17 (14)	6 (17)
During	21 (17)	7 (20)

**TABLE 2**  
**Zoledronic Acid Dosing**

Variables	Interval	
	Standard (n = 121)	Extended (n = 35)
No. doses, mean (SD)	11.4 (13.5)	5.9 (3.18)
Discontinued, No. (%)	121 (100)	21 (60)
Reason for discontinuation, No. (%)		
Adverse reaction	3 (3)	0 (0)
Treatment failure (skeletal-related event)	1 (1)	0 (0)
Dosing interval change	13 (11)	2 (10)
Changed to pamidronate	7 (6)	1 (5)
Death	25 (21)	0 (0)
Patient/physician choice	12 (10)	3 (14.3)
Unknown	61 (50)	16 (76)

performed to correct a fracture or spinal compression. Each SRE was counted as a single occurrence.

Osteonecrosis of the jaw was defined as radiographically documented necrosis of the mandible or associated structures with assessment by a VA dentist. Records from non-VA dental practices were not available for assessment. Documentation of dental assessment before the first dose of ZA and any assessments during treatment were recorded.

Medication use was assessed before and during ZA treatment. Number of ZA doses and reasons for any discontinuations were documented, as was concomitant use of

**TABLE 3**  
**Concomitant Use of Medications**

Medications, No. (%)	Used Before or During Zoledronic Acid			
	Standard-Interval Dosing (n = 121)		Extended-Interval Dosing (n = 35)	
	Before	During	Before	During
Calcium supplement	31 (26)	43 (36)	13 (37)	18 (51)
Ergocalciferol/ cholecalciferol	35 (29)	45 (37)	15 (43)	24 (69)
Calcitonin	1 (1)	0 (0)	0 (0)	0 (0)
Cinacalcet	1 (1)	0 (0)	0 (0)	1 (3)
Calcitriol	1 (1)	2 (2)	0 (0)	0 (0)

**TABLE 4**  
**Patient Outcomes: Overall**

Outcomes	Zoledronic Acid Interval Dosing		
	Standard (n = 121) <sup>a</sup>	Extended (n = 35) <sup>a</sup>	P
Patients with SRE, No. (%)	37 (31)	8 (23)	.374
Skeletal-related events			
Fracture	22 (36)	3 (20)	.172
Spinal compression	9 (14)	2 (13)	.726
Radiation	26 (42)	9 (60)	.598
Surgery	5 (8)	1 (7)	.723
Osteonecrosis of jaw	3 (3)	0 (0)	.347

Abbreviation: SRE, skeletal-related event.

<sup>a</sup>Total number of patients in each group.

calcium supplements, vitamin D supplements, calcitriol, paricalcitol, calcitonin, cinacalcet, and pamidronate.

The primary study outcome was observed difference in incidence of SREs between standard- and extended-interval dosing of ZA. Secondary outcomes included difference in incidence of ONJ as well as incidence of SREs and ONJ by disease subtype (MM, CaP).

Descriptive statistics were used to summarize demographic data and assess prespecified outcomes. Differences in rates of SREs and ONJ between dosing interval groups were analyzed with the Pearson  $\chi^2$  test. The predetermined a priori level of significance was .05.

## RESULTS

Of the 300 patients prescribed ZA at the Memphis VAMC, 177 were excluded (96 for indication, 78 for receiving only 1 dose of ZA, 3 for not

receiving any doses of ZA). The remaining 123 patients were stratified into a standard-interval dosing group (121) and an extended-interval dosing group (35). Of the 123 patients, 33 received both standard- and extended-interval dosing of ZA over the course of the study period and were included discretely in each group for the duration of each dosing strategy. In each group, the ratio of CaP to MM patients was 5:1. The standard-interval dosing group mean age was 69 years and was 98% male and 62% African American; the extended-interval dosing group mean age was 68 years and was 97% male and 71% African American (Table 1).

Pre-ZA dental screenings were documented in 14% of standard-interval patients and 17% of extended-interval patients, and during-ZA screenings were documented in 17% of standard-interval patients and 20% of extended-interval patients. Chi-square analysis revealed no significant difference in rates of dental screening before or during use of ZA.

Standard-interval patients received a mean (SD) 11.4 (13.5) doses of ZA (range, 2-124). Extended-interval patients received a mean (SD) of 5.9 (3.18) doses (range, 2-14). All standard-interval patients had discontinued treatment at the time of the study, most commonly because of death or for an unknown reason. Sixty percent of extended-interval patients had discontinued treatment, most commonly because of patient/physician choice or for an unknown reason (Table 2). The bone-modifying agents used most commonly both before and during ZA treatment were calcium and vitamin D supplements (Table 3).

Skeletal-related events were observed in 31% of standard-interval patients and 23% of extended-interval patients. There were no statistically significant differences in SRE rates between groups ( $P = .374$ ). The most common SRE in both groups was bone irradiation (42% and 60%, respectively), with no statistically significant difference in proportion between groups (Table 4). ONJ occurred in 3% of standard-interval patients and 0% of extended-interval patients. There were no statistically significant differences in ONJ rates between groups ( $P = .347$ ) or in rates of SREs or ONJ within the MM and CaP subgroups (Table 5).

## DISCUSSION

This retrospective review of patients with MM and CaP receiving ZA for bone metastases

TABLE 5

**Patient Outcomes: Multiple Myeloma and Prostate Cancer Subgroups**

Outcomes, No. (%)	Multiple Myeloma ZA Interval Dosing			Prostate Cancer ZA Interval Dosing		
	Standard (n = 21)	Extended (n = 7)	P	Standard (n = 100)	Extended (n = 28)	P
Skeletal-related event	9 (43)	1 (14)	.172	28 (28)	7 (25)	.753
Osteonecrosis of jaw	1 (5)	0 (0)	.557	2 (2)	0 (0)	.451

Abbreviation: ZA, zoledronic acid.

found no differences in the rates of SREs when ZA was dosed monthly vs every 3 months. Although this study was not powered to assess noninferiority, its results reflect the emerging evidence supporting an extension of the ZA dosing interval.

Earlier studies found that ZA can decrease SRE rates, but a major concern is that frequent, prolonged exposure to IV bisphosphonates may increase the risk of ONJ. No significant differences in ONJ rates existed between dosing groups, but all documented cases of ONJ occurred in the standard-interval group, suggesting a trend toward decreased incidence with an extension of the dosing interval.

### Limitations

This study had several limitations. Geriatric African American men comprised the majority of the study population, and patients with MM accounted for only 22% of included regimens, limiting external validity. Patient overlap between groups may have confounded the results. The retrospective design precluded the ability to control for confounding variables, such as concomitant medication use and medication adherence, and significant heterogeneity was noted in rates of adherence with ZA infusion schedules regardless of dosing group. Use of medications associated with increased risk of osteoporosis—including corticosteroids and proton pump inhibitors—was not assessed.

Assessment of ONJ incidence was limited by the lack of access to dental records from providers outside the VA. Many patients in this review were not eligible for VA dental benefits because of requirements involving time and service connection, a reimbursement measurement that reflects health conditions “incurred or aggravated during active military service.”<sup>18</sup>

The results of this study provide further support for extended-interval dosing of ZA as a potential method of increasing patient adherence and decreasing the possibility of adverse drug

reactions without compromising therapeutic benefit. Further randomized controlled trials are needed to define the potential decrease in ONJ incidence.

### CONCLUSION

In comparisons of standard- and extended-interval dosing of ZA, there was no difference in the incidence of skeletal-related events in veteran patients with bone metastases from MM or CaP.

### Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

### Disclaimer

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