Retrospective Comparison of Zoledronic Acid and Denosumab for Prevention of Skeletal Related Events in Multiple Myeloma

Euan A. Forrest[1*], Ethan A. Wetzel[1*], Justin J. Kim[1], Lauren Corliss[2], Zsombor T. Gal[1], Andrew J. Yee MD[1], Ganesh Shankar MD PhD[1]
[1]Mass General Brigham, Harvard Medical School, Boston, MA
[2]University of North Carolina School of Medicine, Chapel Hill, NC
*Co-first author
Presenting Author: Euan A. Forrest (euan_forrest@hms.harvard.edu)

DISCLOSURES: None.

INTRODUCTION: Skeletal-related events (SREs), including pathological fractures, spinal cord compression, bone radiation, or orthopedic surgical interventions, are a major source of morbidity in patients with multiple myeloma (MM), a hematological malignancy of bone marrow causing osteolytic disease. Amongst SREs, axial skeleton pathology, notably vertebral compression fractures (VCFs), are common and often clinically significant[1]. Zoledronic acid (ZA), a bisphosphonate, has long been the standard for SRE prevention, while denosumab, a monoclonal antibody to RANKL, is a newly approved alternative as of 2018. Phase III clinical trials have demonstrated non-inferiority of denosumab to zoledronic acid for time to first SRE[2]. However, a head-to-head analysis of the incidence of SREs and VCFs in individuals with MM while on these bone-modifying agents (BMAs) has yet to be investigated outside of trial conditions and thus was the goal of this study. SREs of the whole skeletal system were assessed, but a sub-analysis of VCFs was done given the relatively high frequency of VCFs compared to other SREs in patients with MM.

METHODS: Under IRB approval, records from a convenience sample of 384 patients (M/F 204/180) diagnosed with MM between 1/1/2002 and 4/15/2025 were retrospectively reviewed. Each patient was treated at Mass General Brigham with a confirmed MM diagnosis and BMA usage. Median age at diagnosis was 65.4±11.6 years of age (range 25.1-92.2). Data on demographics, BMA usage, presence of osteoporosis and bony lesions at the time of diagnosis, time to first SRE, total number of SREs, and types of SREs were collected. Incidence rates were compared using incidence rate difference. Time to SRE was calculated based on time from BMA start. Multivariable modeling was done using multiple linear regression. Alpha of 0.05 was used to determine statistical significance.

RESULTS: We identified 384 multiple myeloma patients with a median of 6.32 years of follow-up. 250 (65.1%) of patients had at least 1 SRE. A total of 1002 SREs were identified and categorized as pathological fractures, orthopedic procedures, and radiation treatment to bone lesions with 769 (76.7%), 166 (16.6%), and 67 (6.7%) of each type, respectively. VCFs accounted for 549 of the 1002 total SREs (54.8%). The median time to first SRE was 3.89 years. Of the 384 patients, 112 (29.2%) received denosumab only, 110 (28.6%) received ZA only, and 162 (42.2%) received ZA and were switched to denosumab. The incidence of SREs was found to be 0.21 SREs per year of denosumab treatment versus 0.53 SREs per year of ZA treatment ($p < 0.0001$, 95% CI of Incidence Rate Difference = 0.28, 0.41). Denosumab was also associated with decreased incidence of VCFs, with denosumab patients experiencing 0.10 VCFs per year of treatment versus 0.23 VCFs per year of treatment with ZA ($p < 0.0001$, 95% CI of Incidence Rate Difference = 0.096, 0.181). In the subset of patients who only received denosumab or ZA and did not cross over, the incidence of SRE was 0.38 and 1.17 SREs per year, respectively ($p < 0.0001$, 95% CI of Incidence Rate Difference = 0.66, 0.93). Patients who received only denosumab had a longer time to first SRE (median not reached) compared to patients who only received ZA (2.03 years) or patients who received both ZA and were later switched to denosumab (5.71 years) (ZA only vs denosumab only: HR = 0.37, p = .0091, 95% CI of HR = 0.22, 0.62; Figure 1). In a multivariable analysis adjusting for time on BMA, the presence of osteoporosis at MM diagnosis, age at MM diagnosis, diagnosis before/after 2018, sex, and the presence of osteolytic lesions at diagnosis, denosumab use was found to be a significant, independent predictor of lower SRE and VCF risk compared to ZA use (SRE: OR = 0.31, p = 0.005; VCF: OR = 0.37, p = 0.002; Table 2).

DISCUSSION: In this retrospective analysis, denosumab was associated with a significantly lower incidence of overall SREs and VCFs compared to ZA. Patients receiving denosumab also experienced a longer time to first SRE. These findings are consistent with prior clinical trials which demonstrated non-inferiority of denosumab to ZA in SRE prevention in MM[2], but our data suggest a superior effect in real world skeletal outcomes which are a frequent cause of morbidity and impaired quality of life in this population.

SIGNFICANCE/CLINCAL RELEVANCE: The reduced incidence of SREs has important orthopedic implications, as pathological fractures such as VCFs often lead to significant pain, loss of functionality, and the need for surgical intervention. This study supports the use of denosumab over ZA as the first-line BMA in patients with MM to mitigate risk for SREs, specifically VCFs. Optimizing BMA selection can thus influence both medical and surgical management strategies to lessen the burden the burden of disease in this patient population, underscoring the need for multidisciplinary, coordinated care between hematology/oncology and orthopedic teams to prevent SREs and improve patient outcomes.

REFERENCES:

1. Melton LJ, 3rd, Kyle RA, Achenbach SJ, et al. 2005. Fracture risk with multiple myeloma: a population-based study. J Bone Miner Res 20:487-493.
2. Raje N, Terpos E, Willenbacher W, et al. 2018. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 19:370-381.

Table 1. Patient Demographics and Skeletal-Related Events in Multiple Myeloma Cohort

Total patients	384
Sex, n (%)	
Male	204 (53.1%)
Female	180 (46.9%)
Age at diagnosis, mean ± SD	65.4 ± 11.6
Age range at diagnosis	25.1 – 92.2
Treatment group, n (%)	
ZA only	110 (28.6%)
Denosumab only	112 (29.2%)
ZA then Denosumab	162 (42.2%)
SREs (VCFs)	1002 (549)
Pathological fractures	769
Orthopedic surgical interventions	166
Radiation to bone lesions	67

Table 2. Multivariable Analyses

Variable	Outcome = Total SREs			Outcome = Total VCFs		
	OR	95% CI of OR	P	OR	95% CI of or	P
Time on BMA	1.04	0.89, 1.21	0.573	1.0779	0.96. 1.20	0.198
Age at MM Diagnosis	0.96	0.92, 0.99	0.043*	0.9714	0.94, 0.99	0.028*
Osteoporosis at MM Diagnosis	1.39	0.81, 2.32	0.218	2.098	1.18, 4.79	0.113
Gender (ref = male)	0.58	0.24, 1.36	0.211	0.7334	0.39, 1.41	0.358
Osteolytic Lesions at Diagnosis	2.55	0.99, 6.18	0.045*	1.5793	0.81, 3.21	0.176
Denosumab Treatment (ref = ZA)	0.31	0.14, 0.73	0.005*	0.3727	0.21, 0.72	0.002*
Date of Dx Before 2018 (ref = after 2018)	0.63	0.27, 1.43	0.267	0.6132	0.33, 1.12	0.115

Figure 1. Time to First SRE - ZA vs Denosumab