ELSEVIER

Blood 142 (2023) 6631–6632

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Impact of Bone Modifying Agent Initiation Time, Frequency, and Duration on Skeletal-Related Events in Patients with Multiple Myeloma

Tyler B. Sandahl, PharmD[1], *Uzoamaka Abajue, PharmD*[2], *Rachel Bubik, PharmD*[1], *Kristin Mara, MS*[1], *Shaji Kunnathu Kumar, MD*[3]

[1] Mayo Clinic, Rochester, MN
[2] Houston Methodist Hospital, Houston, TX
[3] Division of Hematology, Mayo Clinic, Rochester, MN

Background: Skeletal related events (SREs) including pathologic fractures, surgery or radiation to bone, and spinal cord compression contribute to diminished quality of life in patients with multiple myeloma. Bone modifying agents (BMA) such as denosumab or the bisphosphonates zoledronic acid and pamidronate, are used to inhibit osteoclast activity to prevent SREs. The Bone Working Group of the International Myeloma Working Group suggests monthly administration of zoledronic acid for 12 months in newly diagnosed myeloma patients. This is followed by an option to discontinue or decrease administration frequency to every 3, 6, or 12 months if a very good partial response or better is achieved. The ideal start time of BMA from diagnosis and the duration of administration has not been adequately established to optimize reduction of SREs.
Methods: This was a retrospective, single-center study that included newly diagnosed myeloma patients treated at the Mayo Clinic between 9/1/2018 and 9/1/2020 who had received at least one dose of a BMA. The primary objective was to evaluate the impact of BMA dosing frequency and duration on SREs. Secondary objectives included time to BMA initiation, time to relapse or progressions following BMA start, and safety.
Data was summarized using frequencies and percentages for categorical data, and medians and interquartile ranges (IQR) for continuous data. A spline plot and cut-point analysis were used to assess the association of time from multiple myeloma diagnosis to BMA initiation with skeletal related outcomes. Rates of SREs were estimated using the Aalen-Johansen method, where death was treated as a competing risk. Associations of factors with SREs were assessed using Cox proportional hazards regressions, and these associations were summarized using hazard ratios (HR) and corresponding 95% confidence intervals (CI). Variables that could change throughout follow-up including BMA frequency, cumulative BMA dose, and duration of BMA were treated as time-dependent covariates in the Cox proportional hazards models, where the information for these variables was updated each time an additional dose of BMA was given. All analyses were performed using SAS version 9.4 software (SAS Institute, Inc.; Cary, NC) and R version 4.2.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).
Results: Sixty-seven patients were included with a median age of 65 years old. The most frequently used BMA was zoledronic acid (88.1%), followed by pamidronate (7.5%), and denosumab (4.5%). Fifty-five patients (82.1%) had bone disease at baseline. Within 2 years of starting BMA, SREs occurred in 42.2% of patients with baseline bone disease and 8.3% of patients without (p=0.054). Median time to BMA initiation after diagnosis was 45 days (IQR 14-105) in patients with baseline bone disease and 87 (IQR 32-496) in patients without. Among the 26 patients with a SRE, median time from start of BMA to SRE was 170 days (IQR 32-496). No significant association was found between time to initiation and development of a SRE (Figure 1).
BMA dosing frequencies of every 3 months and 6 months had a HR for SREs of 1.67 and 0.47, respectively compared to every 1 month, (P-values >0.25). After excluding patients without baseline bone disease, compared to every 1 month dosing, dosing every 3 months and every 6 months increased the risk of SRE, although the differences were not statistically significant (3 months: HR=1.92, 95% CI 0.76-4.88, p=0.17; and 6 months: HR=1.26, 95% CI 0.14-10.94, p=0.84).
Patients without bone disease at baseline remained on BMAs for a median of 1.8 years while patients with bone disease received BMAs for a median of 2 years. There was no statistically significant difference found with varying duration or cumulative dose and SRE development (Table 1).
Relapse or progression occurred in 32.1% of patients within 2 years of starting BMA, while death occurred in 7.5% of patients. Osteonecrosis of the jaw occurred in 1 patient with bone disease at baseline who received zoledronic acid every 3 months for a duration of 596 days.

Conclusions: No significant association between time of BMA initiation, dosing frequency, or duration on development of SREs were observed. This suggests delaying the start time of BMAs to allow for dental clearance and initial treatment would not increase risk of SREs. Prospective trials are needed to confirm these findings.

Disclosures Sandahl: *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees.

Figure 1. Skeletal Related Events Spline Plot

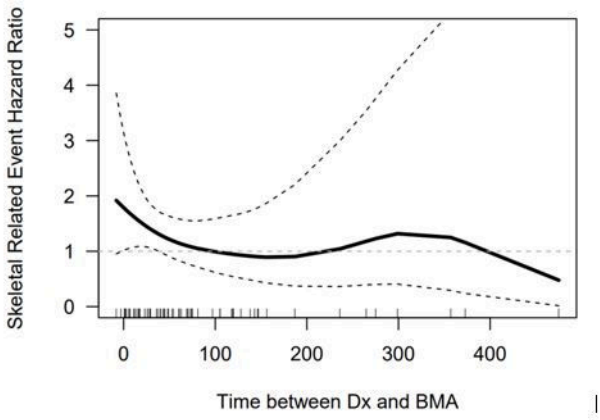

Table 1. BMA Frequency, Duration, and Cumulative Dose on SRE Risk

	Total Population		Bone Disease at Baseline	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
BMA frequency				
1 month	Reference		Reference	
3 months	1.67 (0.66-4.22)	0.27	1.92 (0.76-4.88)	0.17
6 months	0.47 (0.06-3.84)	0.48	1.26 (0.14-10.95)	0.84
BMA duration (per an additional 30 days)	0.94 (0.85-1.04)	0.21	0.91 (0.81-1.02)	0.10
Cumulative dose (per an additional 4 (units))	0.99 (0.96-1.02)	0.40	1.00 (0.98-1.01)	0.59

Figure 1

https://doi.org/10.1182/blood-2023-179319