Incidence and prevention of skeletal related events in multiple myeloma patients: A population based real-world experience

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ABSTRACT

Objectives: Novel treatments in multiple myeloma (MM) could influence the incidence of skeletal related events (SREs). We aimed to examine the incidence of SRE and the preventive use of osteoclast inhibitors (OIs) in a cohort of MM patients in the era of modern treatment.

Methods: In this real-world retrospective study we included patients with a diagnosis of MM between 1.1.2010 and 31.12.2019 with follow-up at St. Olavs University Hospital. Data was extracted from The Myeloma Registry of Central Norway.

Results: SREs occurred in 46% of patients at baseline and 55.8% during follow-up, corresponding to an incidence rate of 29 (95%CI: 26-33) per 100 PY. 48% experienced >1 SRE, and 54% of SREs occurred 30 days before or after starting a new treatment line. The first 2 years after diagnosis 80% received BPs. A higher cumulative dose of BPs showed no significant reduction in incidence of SREs. 20% received supplementation with calcium and vitamin D. Only 2 cases (1.2%) of symptomatic hypocalcaemia and 1 case (0.6%) of osteonecrosis of the jaw were identified.

Conclusion: SREs are still a common problem in an era of novel treatment. Treatment with BPs showed no significant reduction in SREs but was safe in this population.

KEYWORDS

Multiple myeloma - Skeletal related events - Osteoclast inhibitors – Bisphosphonates – Denosumab - Hypocalcemia – Osteonecrosis of the jaw – Calcium and vitamin D – Epidemiology

1 INTRODUCTION

Multiple myeloma (MM) is a hematological malignancy in the bone marrow, with proliferation of clonal plasma cells and the presence of monoclonal proteins in serum and/or urine. MM has the second highest incidence among hematological malignancies (1). The risk of developing MM increases with age, with a median age of onset of 71 years in the Norwegian population (2). There is still no curative treatment, but the introduction of novel therapies has led to deep treatment responses, disease control and improved survival (1, 2, 3). In the population of the Nordic countries, survival has increased in all age groups, including the population above 75 years (2, 4).

MM differs from other hematological cancers in the destruction of bone in the proximity of cancer cells (5), and up to 80% of MM patients present with osteolytic bone lesions at diagnosis (6, 7). The pathophysiology of MM bone disease (MBD) is the uncoupling of the bone-remodeling process caused by the malignant plasma cell (5, 7). Bone lesions increase the risk of skeletal-related events (SREs), defined as pathological fractures, spinal cord compression, or need for surgical or radiotherapeutic intervention (7, 8). SREs can lead to serious suffering for many patients. It impacts their outcome, by narrowing down the therapeutic alternatives, decreasing quality of life (QoL) and overall survival rate (9, 10), along with increasing healthcare-associated costs (11). Therefore, prevention of SREs is important, and can be achieved by using osteoclast inhibitors (OIs), including bisphosphonates (BPs) or denosumab, a monoclonal antibody against RANK-ligand (12, 13, 14, 15). Two potential adverse drug events of OIs are hypocalcemia and osteonecrosis of the jaw (ONJ) (7, 16). In a landscape where myeloma treatment improves rapidly and possibly also impacts MBD, our primary aim was to examine the incidence of SREs along with the use of OIs as prophylaxis, in a cohort of Norwegian myeloma patients in the era of novel drugs.

2 METHODS

2.1 Data sources

Information on all MM cases was provided from The Myeloma Registry of Central Norway (MRCN). The MRCN has a coverage of >95 % of all patients with MM in the region. We included data on baseline characteristics, lines of myeloma treatment, progression, SREs, laboratory values, ONJ and OI administration.

2.2 Study population

All cases of MM (ICD-10: C90.00) in the period 1.1.2010-31.12.2019, with an entry in the MRCN and with follow-up at St. Olav University Hospital, were included in the study. Patients were followed until death or until a final cut-off of 31.12.2021. We excluded patients with the diagnosis of smoldering myeloma.

2.3 Definitions

All SREs registered in the MRCN are based on review of electronic health records. In the MRCN the SREs are defined in accordance with international guidelines (7, 8). We classified SREs occurring within 60 days prior to or after MM diagnosis as baseline SREs. SREs were defined as the same event if they occurred within 21 days and were in the same skeletal area (vertebral column, costa, sternum, clavicle, pelvis, cranium, upper or lower extremity), to ensure that interconnected events were not counted as distinct SREs. This definition is based on previousSREs in MM patients (17, 18). An SRE between two treatment lines was placed in the previous line's group. Disease progression was defined according to IMWG criteria (19).

We defined hypocalcemia as serum corrected calcium < 2.20 mmol/L (<8.8 mg/dl) (20, 21), and graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0 (22) For the patients given BPs we registered the lowest value of serum total calcium within the first 3 months after initiation if serum total calcium was below the lower reference range (< 2.15 mmol/L) of the local laboratory (<2.15 mmol/L). For patients with low serum total calcium, we registered serum albumin to calculate corrected calcium with the formula: serum calcium (mmol/L) + 0.02 (40 – serum albumin (g/L))(20, 23). Due to lack of documented albumin value, serum total calcium was used in 18 patients while ionized calcium level was used in 1 patient.

To investigate the use of OIs, we registered the doses administered in the outpatient clinic. Records of calcium and vitamin D supplementation were incomplete. Therefore, supplementation was registered as

present, if mentioned in health records at any point, prior to or after MM diagnosis. Only two patients received Denosumab, one of them due to osteoporosis. Hence, they were excluded from analyses results regarding hypocalcemia and ONJ.

2.4 Statistical methods

We used the statistical program SPSS (IBM statistics, version 28.0.1.0(142)) to perform descriptive analyses and Spearman's rank correlation to assess the relationship between cumulative dose of BPs and incidence of SREs. To adjust for different lengths of follow-up time in our correlation analyses, we calculated the percentage of recommended cumulative dose of BPs for the first 2 years (Norwegian guidelines 2012-2021), and the mean dose of BPs per month of the total follow-up time. For the variable “incidence of SREs”, we excluded baseline SREs and calculated the mean number of SREs per month of follow-up after baseline. Bootstrapping was used for 95% CI. Incidence rates was calculated by dividing the sum of SREs by the total follow-up time for the study population for the periods of interest. Poisson Rate Confidence Interval was used for confidence intervals.

2.5 Ethical approval

The project was approved by the Regional Committee for Medical and Health Research Ethics (399801) and the scientific committee of the MRCN. All living patients included in the MRCN have signed an informed consent for the use of their clinical data in medical research. We received an exemption from informed consent for patients who were dead at the time of inclusion in the MRCN.

3 RESULTS

Baseline characteristics of the study population at diagnosis, including 199 patients, with a predominance of men, are shown in Table 1. Median age at diagnosis was 69 years (range 34-92). Median follow-up time from after the baseline period was 41 months (range 0-141). A previous history of low energy fracture and/or osteoporosis and/or treatment of osteoporosis was recorded in recorded in 12-13%. 73% of patients had 1 or more osteolytic lesions on imaging at diagnosis. In 32 patients there were unknown/uncertain radiological findings. Treatment with BPs was started in 57% within 3 months of diagnosis. View table 1 for further baseline characteristics.

TABLE 1. Baseline characteristics. Follow-up time is calculated from 60 days after diagnosis to exclude the baseline period. Hypercalcemia is defined as albumin corrected calcium > 2.51 mmol/ L.

	Cohort (n=199)
Sex, N (%)	
Male	121 (60.8)
Female	78 (39.2)
Age at diagnosis, years	
Median (range)	69 (34-92)
Follow-up length, months	
Median (range)	43 (0-143)
Previous low energy fracture, N (%)	
Yes	26 (13.1)
Previous osteoporosis, N (%)	
Yes	25 (12.6)
Previous treatment of osteoporosis, N (%)	
Yes	24 (12.1)
Radiological findings at diagnosis, N (%)	
One or more osteolytic lesions	122 (73.1)
None	45 (26.9)
Unknown/ uncertain findings	32
Bisphosphonates within 3 months of index date, N (%)	
Yes	114 (57.3)
Hemoglobin at diagnosis, g/dl	
Median (range)	11.3 (5.3-16.4)
Creatinine at diagnosis, μmol/L	
Median (range)	83 (29-1526)
Albumin corrected calcium at diagnosis, mmol/L	
Median (range)	2.39 (2.10-4.72)
Hypercalcemia, N (%)	56 (29.6)

3.1 Skeletal related events

During the study period, 348 SREs occurred, with a mean of 1.75 (95%CI: 1.51-2.01) events per patient. The incidence rate was 40 (95%CI: 36-45) per 100 PY. At least one SRE occurred in 143 of the 199 patients (72%) (Table 2). Only 28% recorded no SREs at all, while 48% experienced more than 1 SRE. 47% of SREs occurred during treatment, and 54% within 30 days before or after starting a new treatment line. Pathological fractures were the most frequent SRE and accounted for 70%, followed by radiation therapy (19%), and spinal cord compression (10%). Surgical treatment alone was rarely used (1%) (Figure 1). Baseline was the period with the highest occurrence of SREs, with an incidence rate of 173 (95%CI: 143-208) per 100 PYs. The lowest incidence was found in treatment line 1, with an incidence rate of 18 (95%CI:14-23) per 100 PYs, followed by a gradual increase to 148 (95%CI: 103-207) per 100 PYs in treatment line 6+. There was no significant difference between the groups of patients diagnosed in the time periods 2010-2014 and 2015-2019 (Figure 2). 34% of the patients who died during follow-up, experienced an SRE after initiation of their final line of treatment. During the total follow-up time (baseline SREs excluded), SREs occurred in 55.8% of the study population, and the incidence rate was 29 (95%CI: 26-33) events per 100 PY. The incidence rate was higher in patients ≥ 70 years at diagnosis, compared to <70 years (Table 2).

TABLE 2. Incidence of skeletal related events (SREs). Baseline defined as the period 60 days prior to and after diagnosis.

	Total (95% CI)	**Baseline excluded (95% CI)**
Sum (N = 199)	348	233
Mean	1.75 (1.51-2.01)	1.18 (0.97-1.40)
Incidence rate (total), per 100 PY	40 (36-45)	29 (26-33)
< 70 years (N = 103)	36 (31-41)	26 (22-31)
≥ 70 years (N = 96)	48 (41-56)	34 (28-42)

FIGURE 1. Distribution of SREs by type. N = number of patients experiencing each type.

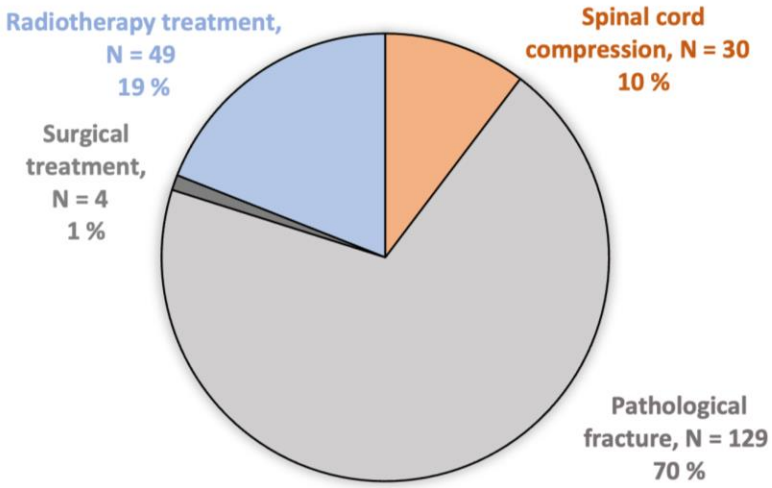
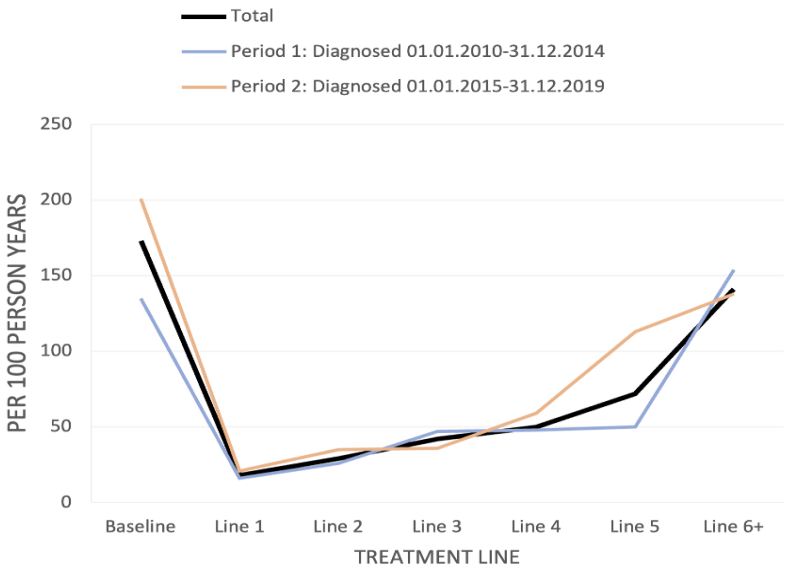


FIGURE 2. Incidence rate of SREs by treatment line. Baseline includes SREs 60 days prior to or after diagnosis. Baseline SREs that occurred in line 1 were included as baseline and subtracted from line 1. Time period for each treatment line was calculated from start treatment line until start next treatment line, final cut-off of (31.12.2021) or death.



Numbers at risk							
Total	199	197	149	101	80	59	33
Period 1	78	78	68	51	38	31	18
Period 2	121	119	79	49	40	28	15

3.2 Osteoclast inhibitors

During the first 2 years after diagnosis, 159 of 199 patients (80%) received BPs, with a mean of 10 doses (95% CI: 9-11), ranging from 1-24. Several patients switched from Pamidronic acid (PA) to Zoledronic acid (ZA) during treatment. 2 patients received Denosumab. According to Norwegian recommendations in the period 2012-2021, patients should receive monthly doses of OIs the first 2 years (24 doses in total). The patients in our cohort received an average of 41.9% of this (24, 25). Almost all the patients treated with BPs, started within the first 2 years. During the complete time of follow-up, the mean total number of doses was 17 (95%CI: 15-19) for the entire population. The mean number of doses per month of follow-up was 0.42 (95%CI:0.38-0.46). The use of BPs is shown in table 3. 7.4% experienced a dose reduction during treatment.

TABLE 3. Use of bisphosphonates during the first two years after diagnosis and for the total follow-up time. N (%) = number and proportion of patients. Mean = mean dose of BPs. Percentage of recommended dose is based on Norwegian guidelines (2012-2021), which recommend BPs monthly for the first 2 years after diagnosis. 24 doses = 100%.

	N (%)	Mean (95%CI)	Range
First 2 years			
Total number of doses with BPs	**159 (79.9)**	**10.0 (9.1-11.0)**	**1-24**
Zoledronic acid	**88 (44.2)**		
Number of doses		*9.2 (7.7-10.8)*	*1-24*
Cumulative dose (1 dose = 4 mg)		*38.4 (31.8-45.3)*	*4.0-176.0 mg*
Pamidronic acid	**104 (52.3)**		
Number of doses		*8.0 (7.0-9.0)*	*1-20*
Cumulative dose (1 dose = 30 mg)		*239.4 (208.0-272.0)*	*15.0-690.0 mg*
Proportion of recommended dosage		**41.9% (37.8-46.1%)**	**2.1-100%**
Total follow up time			
Total number of doses with BPs	**162 (81.4)**	16.7 (14.9-18.5)	1-42
Zoledronic acid	**110 (55.3)**		
Number of doses		*13.8 (11.9-15.8)*	*1-37*
Cumulative dose (1 dose = 4 mg)		*54.4 (46.5-62.2)*	*4.0-148.0 mg*
Pamidronic acid	**104 (52.3)**		
Number of doses		*11.7 (10.0-13.3)*	*1-33*
Cumulative dose (1 dose = 30 mg)		*350.5 (299.1-401.0)*	*15.0-990 .0 mg*
Mean number of doses/ months		**0.43 (0.39-0.47)**	**0-1.1**

3.3 Bisphosphonates and SREs

There was no statistically significant correlation between the cumulative dose of BPs the first 2 years after diagnosis, and the incidence of SREs (r=.03, N=159, p=.680) when only patients receiving BPs were included. There was however, a weak, but statistically significant, positive correlation between a higher cumulative dose of BPs given during the total follow-up time, and a higher incidence of SREs (r=.18, N=162, p=.019). When the whole study population was included, there was a weak, but statistically significant positive correlation between a higher incidence of SREs and a higher cumulative dose of BPs during the first 2 years after diagnosis (r=.17, N=199, p=.016). This correlation also held true for the entire population for the total follow-up time (r=.29, N=199, p=< .001).

3.4 Calcium and osteonecrosis of the jaw

Calcium supplementation with or without vitamin D was mentioned in the charts of 20% of the patients included in this study. For the remaining 80%, supplements were not mentioned at all. In 53 patients (33%) given BPs, we found calcium below the reference range within 3 months of starting BP therapy. According to CTCAE 5.0, most of these cases (45) were mild. One event was graded as life-threatening (grade 4) based on laboratory values, although the patient did not have any symptoms. Only 2 symptomatic cases with need for treatment were identified. The incidence rate of hypocalcaemia was 131 (95%CI: 98-171) per 100 PY. ONJ occurred in 1 patient (0.6%), and the incidence rate was 15 (95%CI: 0-85) per 10 000 PY (Table 4).

TABLE 4. Frequency of calcium and vitamin D supplementation, hypocalcemia and osteonecrosis of the jaw. Supplementation was registered as yes if given at some point, prior to or after diagnosis. Both calcium alone and combined with vitamin D was registered. Hypocalcemia was defined as albumin corrected calcium < 2.20 mmol/L and graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0. The case of osteonecrosis of the jaw was CTCAE grade 3.

	Yes, N (%)	**No, N (%)**
Calcium and vitamin D supplementation	**40 (20)**	**159 (80)**
Hypocalcemia within 3 moths after start BPs	**53 (33)**	**109 (67)**
CTCAE Grade 1 (mild)	45	
CTCAE Grade 2 (moderate)	5	
CTCAE Grade 3 (severe)	2	
CTCAE Grade 4 (life-threatening)	1	
CTCAE Grade 5 (death)	0	
Osteonecrosis of the jaw	**1 (0.6)**	**161 (99.4)**

4 DISCUSSION

In this real-world retrospective cohort study, we investigated the incidence of SREs and use of BPs in 199 patients with MM and follow-up at St. Olavs Hospital, where all patients with MM in the region are treated. Baseline SREs occurred in 46%, and this was the period with the highest frequency. During the follow-up time (baseline excluded), SREs occurred in 55.8% of the study population with an incidence rate of 29 (95%CI: 26-33) per 100 PY. Pathological fractures were the most frequent type and accounted for 70%. 48% experienced more than 1 SRE, and 54% of SREs occurred 30 days before or after starting a new treatment line. During the first 2 years after diagnosis, 80% received BPs. A higher cumulative dose of BPs, showed no significant reduction in incidence of SREs, but was rather associated with a higher incidence of SREs. Most of the population did not receive any supplementation with calcium and/or vitamin D, but only 2 cases of hypocalcemia requiring treatment were identified in our study population. ONJ occurred in only 1 of the patients (0.6%).

Real-world studies from the USA, Greece, and the Republic Korea, have investigated the incidence of SREs in the last decade, and our results are in concordance with these data (11, 17, 26, 27). Other studies have also found that pathological fractures are the most frequent type of SRE (17, 26, 28). Our study, alongside the study by Baek *et al*, shows an increased risk of SREs with increasing patient age (18).

54% of SREs occurred 30 days before or after starting a new treatment line, supporting the current consensus that SREs are a sign of MM progression. Conversely, this means that nearly 50% of the SREs did not occur in relation to starting a new line of treatment. This is probably due to fractures not judged as disease progression by the treating physician. Since regular CT-scans are not standard follow-up in myeloma, we do not know if these SREs were preceded by progressive bone disease. A soon to be published paper by the Nordic Myeloma Study Group, indicates that regular pre-planned bone imaging can identify progressive bone disease earlier than standard follow-up today (personal correspondence with Tobias Slørdahl).

Almost half of our study population experienced more than one SRE. This is consistent with other studies that suggest having a history of SREs increases the risk of new events (17, 28). Figure 2 shows the occurrence of SRE during the disease course. The highest incidence of SREs was found during the baseline period followed by a low occurrence in treatment line 1. This aligns with previous studies showing that most bone complications occur early in the disease course (13, 17, 28). In addition, we found a gradual

increase in SREs from treatment line 1 to 6+, consistent with the database study from oncology clinics in United States showing an increase in SREs in each subsequent line (17).

In our study, BPs were given to 80% of the patients, which is higher than in comparable cohorts in Denmark (29) and the Republic of Korea (27), but similar to the chart review of 5 countries by Mateos *et al* (28). ZA was the most frequently used BP in our cohort, consistent with guidelines from 2015 (30), recommending ZA as the first option, due to superior overall survival (OS) compared to clodronate (12).

Our population received fewer doses of BPs than recommended by the Norwegian guidelines. This may be influenced by changes of recommendations in the inclusion period (24, 25). Discontinuation of BPs due to decrease in kidney function may be another reason for the low number of doses. BPs is not recommended for patients with GFR below 30 ml/min, and in this group Denosumab is a reasonable option due to its extrarenal clearance (8). Denosumab was first recommended in Norwegian guidelines in 2018 (31). Overall, 20% had no record of treatment with BPs and only 2 patients received Denosumab. This suggests an unmet need, especially in patients with reduced kidney function or lack of detectable bone disease.

However, we found no evidence that increasing the amount of BPs lead to a reduction of SREs in our study population. We did correlation analyses both including the whole study population and only including patients given BPs. A higher cumulative dose of BPs was associated with more SREs, most pronounced in the analysis including the whole population. National guidelines recommend reinitiating BPs with relapse of active bone disease, which probably explains most of this association (24). The results also suggest a low incidence of SREs among patients not treated with BPs, supporting the physician's decision to abstain from treatment. Despite explicit national guidelines, there are still different opinions concerning treatment with BPs in patients without detectable MBD. Further prospective studies comparing the effect of different dose regimens are warranted.

Supplementation with calcium was only mentioned in the health records of 20% of patients. IMWG and ESMO recommend supplementation to all patients receiving OIs to prevent severe hypocalcemia (7, 8) However, Norwegian guidelines have not yet mentioned supplementation (24). In our study, we found only 2 symptomatic cases of hypocalcemia, despite the low use of calcium supplementation. This is in concordance with other studies (32, 33). However, Body *et al* (32) found a lower incidence of hypocalcemia in patients taking supplementation, while a network analysis by Mhaskar *et al* (34) showed no evidence for difference in the incidence of hypocalcemia in patients receiving BPs compared with

placebo or no treatment, or when comparing different BPs. Interestingly, Yerram *et al* (35) found that the most severe cases were not prevented by supplementation of calcium and vitamin D. Our study supports the finding that hypocalcemia is rarely a clinically significant complication of BP use, even when use of calcium supplementation is low.

ONJ occurred in only 1 patient (0.6%) during this study, a lower occurrence than seen in clinical trials. A RCT by Raje *et al*, comparing Denosumab and ZA in MM patients found an incidence of ONJ of respectively 4% and 3% (13). The mean number of doses per month in this study was 0.87, twice as much as in our study with a mean of 0.43. Results from an open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer (36), found an incidence of 1.9% and 1.2% in patients given Denosumab and ZA, respectively, during the blinded treatment phase. In addition, they found higher rates of ONJ with increased exposure to anti-resorptive treatment. The low incidence of ONJ in our cohort may be affected by our population receiving a relatively low number of doses of BPs compared to recommendations and clinical trials.

Our study is a robust real-world study including a population-based cohort representative of the total MM population, including elderly patients and those with comorbidities. The MRCN includes SREs based on a thorough medical record review, not diagnostic or treatment coding. Due to different methods, definitions of SRE, populations and data sources in the studies on SREs in MM patients, the incidence rates and proportions may not be directly comparable. In our study we counted SREs within 21 days in different anatomical areas as separate SREs. We also included patients who died shortly after diagnosis, where SREs were registered by reading through health records rather than based on diagnostic codes. This may have led to a slightly higher incidence in our study compared to other real-world studies. Limitations include human error, and incomplete documentation on supplements with calcium and hypocalcemia in electronic health records.

In conclusion, this study found a high incidence of SREs in a population treated during the recent decade, with access to novel drugs. The incidence is highest at diagnosis and increases again in later treatment lines. A high proportion of patients received OIs, but the number of doses was lower than national recommendations, and few patients received Denosumab. We did not find evidence that increasing the amount of BPs lead to a reduction in SREs, but the use of BPs was safe with few cases of clinical hypocalcemia and ONJ. In the future, studies comparing BP treatment with different dosage and dosing intervals might lead to fewer side effects, lower costs and less time use for patients and health services. The role of calcium and vitamin D supplementation is still unknown in MM treatment.

CONFLICT OF INTERESTS

MSS, MR and KLFM have no competing interests. TSS has received honoraria from Takeda, Celgene, Amgen, and Janssen-Cilag. Consultancy: Bristol Myers Squibb and GSK. Advisory board consultancy: Amgen, Celgene, GSK, and Janssen-Cilag.

AUTHOR CONTRIBUTIONS

All authors designed the study. MSS and MR collected and analysed data and wrote the manuscript. MR preformed the statistical analysis. All authors interpreted the data and critically revised, discussed, and approved the last version of the manuscript.

DATA AVAILABILITY STATEMENT

The data sets analysed during the current study are available from the corresponding author upon reasonable request.

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SUPPLEMENTARY

Table 1. Incidence and distribution of SREs by type. N = number of patients with SRE by type. Sum = total number of SRE by type. % = proportion of patients with SRE by type and distribution of SRE by type (also shown in figure 1 in the article).

	N (%)	Sum (%)
Total	**143 (72)**	**348 (100)**
Spinal cord compression	30 (15)	36 (10)
Pathological fracture	129 (65)	242 (70)
Surgical treatment	4 (2)	4 (1)
Radiotherapy treatment	49 (25)	66 (19)

Table 2. Number and proportion of patients by number of SREs.

Number of SREs	N (%)
0	56 (28.1)
1	48 (24.1)
2	41 (20.6)
3	31 (15.6)
4+	23 (11.5)

Table 3. Proportions of patients with SRE, sum of SREs and incidence rate of SREs by treatment lines. Baseline includes SREs 60 days prior to or after diagnosis. Baseline SREs that occurred in line 1 were included as baseline and subtracted from line 1. Time period for each treatment line was calculated from start treatment line until start next treatment line, final cut-off of (31.12.2021) or death. Incidence rate was not calculated for last line before death.

Period	Patients at risk	Patients with SRE (%)	Sum SREs	Incidence rate per 100 PYs (95%CI)	Minimum – maximum
Total	199	143 (71.9)	348	40 (36-45)	0 - 11
Baseline	199	92 (46.2)	115	173 (143-208)	0 - 3
Total, baseline excluded	197	111 (56.3)	233	29 (26-33)	0 – 8
Line 1	197	53 (26.9)	70	18 (14-23)	0 - 4
Line 2	149	39 (26.2)	48	29 (21-38)	0 - 3
Line 3	101	20 (19.8)	30	42 (28-59)	0 - 3
Line 4	80	18 (22.5)	24	50 (32-74)	0 - 2
Line 5	59	14 (23.7)	24	72 (46-106)	0 - 4
Line 6+	33	15 (45.5)	34	148 (103-207)	0 - 7
Last line before death	117	40 (34.2)	61		0 - 4