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Research Article

Skeletal morbidity rates over time in patients with bone metastases from solid tumors reported in bone modifying agents randomised trials



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ABSTRACT

Objective: Skeletal related events (SREs) are common in patients with bone metastases and lead to decreased quality of life and functional status. The definition of an SRE has evolved over the years and now excludes hypercalcemia of malignancy due to its low incidence. The purpose of this review was to investigate if advances in bone-targeted therapies have decreased skeletal morbidity rates (SMR) over time.

Methods: A literature search was conducted in several databases to identify phase III results from bone-targeted therapy trials from 1980 through September 2011. Graphs were created to document the trends of the natural log of SMR over the mean time of enrolment for all placebo and intervention arms. Statistical hypothesis testing was employed to account for confounding factors.

Results: A total of 14 studies were identified which reported the SMR from phase III trials from 1990 to 2007. A statistically significant downward trend was observed in the placebo arms of trials over time; a similar trend was seen in all intervention arms. In a direct comparison of intervention against placebo arms, it was found that there was a significant decreasing time trend ($p < 0.0001$) and a significant departure in SMR from placebo to intervention arms ($p = 0.0348$). These results were seen even after accounting for the confounding factors of histology and differences in drugs.

Conclusion: The decrease in SMR over time may not only be a result of advancements with bone targeted agents, but also due to better management and awareness of events associated with bone metastases.

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1. Introduction

Metastatic disease in advanced cancer most commonly manifests itself in bone. Of all advanced breast or prostate cancer, 65% to 75% of patients develop metastases to bone, while in patients with other solid tumours 30% to 40% of patients will develop bone metastases [1]. Patients with bone metastases are at a high risk of developing SREs (such as bone pain requiring analgesics or palliative radiation therapy, spinal cord compressions (SCC), pathological fractures, hypercalcemia, or a need for surgery), which can greatly reduce quality of life (QOL) [3]. Retrospective analyses of several tumour types have demonstrated that patients with bone metastases who experience an SRE are more likely to experience subsequent SREs [2]. SREs undermine patients' functioning, beget significant morbidity, and reduce patients' survival. As treatment

intent for patients with advanced cancers shifts from survival to the preservation of QOL, the principal objective becomes the management and prevention of SREs secondary to bone metastases.

"Skeletal-related complications" as a quantifiable clinical end point were first defined as pathologic fractures, irradiation of or surgery on bone, spinal cord compression, or hypercalcemia of malignancy (HCM); they were first applied to studies assessing pamidronate in women with bone metastases from breast cancer [3]. In the past, HCM was highly prevalent in breast cancer patients with bone metastases [3]; but today, it is a condition that is rarely seen due to a better understanding of the disease and the frequent use of anti-resorptive therapies. Therefore, in more recent studies, HCM has been excluded in the standard SRE definition. This is appropriate, as comparisons of HCM rates reported in studies performed in the 1990s show significantly lower rates of HCM than those conducted in the 1970s and 1980s [4]. In a retrospective analysis of patients with breast cancer from 1975 to 1984 who had first recurrence of disease in the bone, 17% developed hypercalcemia [5]. In the placebo arm of a study evaluating the safety of cyclic pamidronate in breast cancer patients, where study enrolment

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began in 1990, the incidence of hypercalcemia in patients with lytic bone disease was 13%, compared with 6% in the pamidronate arm [4].

The introduction of bone targeting agents to patients' treatment has been shown to be beneficial in preventing SREs and reducing pain in large phase III trials. Bone targeted therapies have been found to prolong the time to first SRE and reduce the rate of SREs [6]. The introduction of new anti-resorptive therapies into clinical practice, such as the nitrogen-containing IV bisphosphonate pamidronate early in the 1990s, zoledronic acid from 2000, and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor denosumab in 2010 is accompanied by increased disease state awareness. Consequently, general standards of care in the skeletal health of cancer patients have improved.

Nonetheless, SREs remain a common problem for patients with bone metastases from advanced cancer. As such, curtailing SREs will have benefits for the healthcare system in terms of reduced patient morbidity and lower healthcare costs [7]. The skeletal morbidity rate (SMR) is defined as the ratio of the number of SREs for each subject divided by the subject's time at risk in years. For example, if a study follows 1000 patients for one year and among those 1000 patients 350 SREs occur, then the SMR value would be 0.35 SREs/year. If multiple events are experienced within a year these values are included within the ratio.

This review aims to investigate how developments in bone targeted therapies have affected the incidence of SMRs over time. A trend analysis was performed to examine the SMR from the placebo arms of randomized controlled trials (RCTs) over time, and also the trend in the SMR values from the intervention arms of those RCTs over the same time period.

2. Methods

A literature search was conducted in MEDLINE (OvidSP) (1980 through September 2011), EMBASE (OvidSP) (1980 through September 2011), and Cochrane Central Register of Controlled Trials (OvidSP) (September 2011) to identify phase III results from bisphosphonate and other bone-targeted therapy trials. The following medical subject headings and text words were used: "exp neoplasms", "cancer", "carcinoma", "tumor", "malignan:", "bone neoplasms/sc" (secondary), "bone metast:", "osseous metast:", "bone pain", combined with "exp diphosphonates", "bisphosphonate", "exp alendronate", "alendronate", "alendronic acid", "exp clodronic acid", "clodronic acid", "clodronate", "dichloromethylene", "exp etidronic acid", "etidronic acid", "etidronate", "exp ibandronate", "ibandronate", "ibandronic acid", "pamidronate", "aredia", "exp zoledronic acid", "zoledronic acid", "zolendronate", "zometa", and "denosumab". Those terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The literature search was not restricted by language. Studies were limited to phase III and IV trials involving patients with solid tumours, excluding trials in patients with multiple myeloma. Articles reporting the same population data were excluded.

Results of the search were independently sorted for potential inclusion by 6 coauthors. This process identified 20 eligible studies. The number of SREs that occurred was gathered for all interventions and placebo arms of studies. This included radiation therapy, pathological fractures, spinal cord compression, surgical intervention and hypercalcemia. The articles were further refined, selecting only those that reported SMR. SMR values were the most consistently quoted outcome measure after SRE, in 14 of the 20 identified studies. The SMR was identified to be the primary outcome of interest in this study as it standardizes the rate of skeletal-related events over a time period, typically one year,

where pure numerical events would unequally weigh trials to those with the longest follow-up or largest cohort.

As we were not privy to the median year of enrolment, for all selected studies, the mean enrolment year ($(\text{start of enrolment} + \text{end of enrolment})/2$) was calculated. If these dates were unavailable, the corresponding authors or sponsoring companies were contacted. When all methods to gather this information were exhausted, for studies that did not report their enrolment period, the average of the mean enrolment year for the same intervention drug reported in literature was used. Here, an assumption was made that intervention drugs tend to be tested over approximately the same years. To normalize the distribution of SMR, natural log-transformation was applied. Graphs were created depicting SMR (log-scale) as a function of the year of enrolment for placebo arms and treatment arms. Due to the different enrolment numbers in each study, the SMR log-values were weighed accordingly (also known as weighted least squares). Weighted linear regression modified the standard linear regression model (minimizing the square of the error between predicted value \hat{Y}_i and the actual value Y_i) to $\min \sum_{i=1}^m W_i(Y_i - \hat{Y}_i)^2$, where W_i is the weighted value for each study (known as number of patients per study). These weighted linear regression models over time were constructed and p -values less than 0.05 were considered as statistically significance. Negative coefficients of time (slope) indicate that the average SMR (log-scale) is decreasing over enrolment year. The interaction term for the slopes of placebo versus intervention patients was calculated as well. We also conducted the above models with accounting for histology and/or drug as confounding factors due to heterogeneous studies. Histology was treated as a categorical variable with different primary cancer sites including breast, bladder, lung (other solid tumors), prostate, and renal cell carcinoma. For intervention treatment, different drug mechanism were accounted for, these included denosumab, ibandronate, pamidronate, and zoledronic acid. R^2 was calculated for each model, with higher values of the R^2 demonstrating better model fitting.

This process was repeated while considering histology as a confounding factor for both placebo and intervention arms. For patients treated with intervention, the different drugs used were also considered as a confounding factor. All analysis was conducted by Statistical Analysis Software (SAS version 9.2 for Windows).

3. Results

3.1. Analysis of SMR

A total of 14 studies were identified which reported SMR and the dates of enrolment (Table 1). The majority (7/14) included patients with breast cancer, three of the remaining involved patients with prostate cancer, two with renal cell carcinoma and a single study for each of primary bladder cancer and lung or other solid tumors. Enrolment periods for included studies ranged 17 years, from 1990 to 2007. Most studies identified compared zoledronic acid to placebo.

An overall downward trend was observed in the placebo arms of all studies using the natural log model of SMR (Fig. 1). In the early 1990s, SMRs ranging between 3.0 and 4.0 were not uncommon. After approximately a decade and a half, SMRs were reduced to around a single event per year. This trend was found to be statistically significant with a p -value of 0.0021 with a Pearson's correlation coefficient of 0.63.

During the same time period, statistically significant decreases in SMR were observed in all intervention arms included with a p -value less than 0.0001 with a R^2 of 0.64 (Fig. 2). At its peak in the early 1990s, SMRs ranged between 2.0 and 3.0. From the

Table 1
Studies reporting SMR values ordered by publication date.

Author	Pub year	Enrol start	Enrol end	Primary cancer	Treatment			SMR		
					Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
Theriault [3]	1999	1990	1995	Breast	Pamidronate	Placebo	NA	2.40	3.80	NA
Lipton [4]	2000	1990	1996	Breast	Pamidronate	Placebo	NA	2.40	3.70	NA
Saad [20]	2002	1998	2001	Prostate	Zoledronic acid (4 mg)	Zoledronic acid (8 mg)	Placebo	0.80	1.06	1.49
Rosen [21]	2004	1998	1999	Breast	Zoledronic acid	Zoledronic acid	Pamidronate	0.98	1.06	1.55
Body [22]	2003	NR	NR	Breast	Ibandronate	Ibandronate	Placebo	1.31	1.48	1.19
Lipton [23,24]	2003	NR	NR	Renal Cell	Zoledronic acid	Zoledronic acid	Placebo	2.68	1.67	3.38
Rosen [25]	2004	NR	NR	Lung, solid tumours	Zoledronic acid (4 mg)	Zoledronic acid (8 mg)	Placebo	2.24	1.55	2.52
Tripathy [26]	2004	1996	2000	Breast	Ibandronate (20 mg)	Ibandronate (50 mg)	Placebo	0.97	0.98	1.20
Saad BJU (Renal Subgroup) [27]	2006	NR	NR	Renal Cell	Zoledronic acid	Placebo	NA	2.58	3.13	NA
Saad (Clinical Prostate Cancer) [2]	2007	1998	2001	Prostate	Zoledronic acid	Placebo	NA	0.42	0.88	NA
Saad BJU (Prostate Subgroup) [28]	2005	1998	2001	Prostate	Zoledronic acid	Placebo	NA	0.77	1.47	NA
Kohno [29]	2005	2000	20030	Breast	Zoledronic acid	Placebo		0.63	1.10	NA
Stopeck [7]	2010	2006	2007	Breast	Denosumab	Zoledronic acid	NA	0.45	0.58	NA
Zaghloul [30]	2010	2005	2007	Bladder	Zoledronic acid	Placebo	NA	0.85	2.05	NA

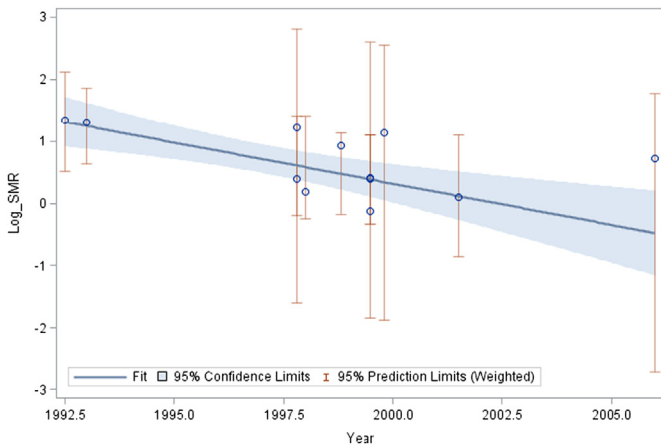


Fig. 1. Skeletal morbidity rates (SMR) over time of placebo arms in phase III trials with weighted linear regression model.

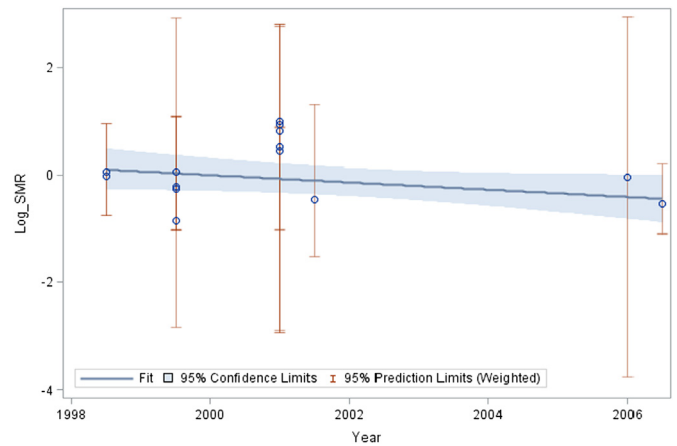


Fig. 3. SMR rates over time of zoledronic acid treatment arms in phase III trials with weighted linear regression model.

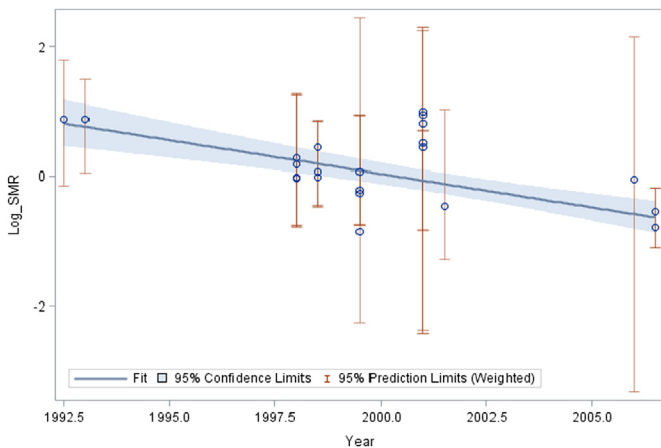


Fig. 2. SMR rates over time of all intervention arms in phase III trials with weighted linear regression model.

latest available data, patients now experience on average less than one event per year. Improvements in SMR were seen in zoledronic acid arms compared to earlier intervention arms. When

looking solely at studies reporting results of zoledronic acid trials relatively stable SMR values were seen across the time period 1990–2007 (Fig. 3). This trend across 14 zoledronic intervention arms indicates that stable benefits were incurred, but with a non-significant decreasing trend ($p=0.0855$; $R^2=0.23$). In zoledronic acid trials, SMRs were consistently around 1.0 events/year (events/year ranged from 0.42 to 2.68). Following relatively stable SMRs across all zoledronic acid trials, a further decrease in SMR is seen in the breast cancer denosumab trial, where a SMR value of 0.45 was found [8].

In a direct comparison of intervention arms against placebo arms (Table 2), it was found that there was a significant decreasing time trend ($p < 0.0001$) and a significant departure in SMR from placebo in intervention arms ($p=0.0348$) (Fig. 4). The non-significant interaction term ($p=0.51$) indicates that the decreasing slope found in placebo or intervention patients are similar. The R^2 for the model was also calculated to be 0.73.

Overall, SMR rates in intervention arms are lower than placebo arms. Further data analyzing factors that could have confounded SRE and SMR values were tabulated. This included primary cancer, primary end point, study duration, percentage of patients

Table 2
Weighted linear regression model of natural log of SMR over time in patients treated with Intervention or with Placebo.

Parameter	Coefficient	Standard Error	p-value
<i>Before accounting for confounding factors</i>			
Intercept	215.7770	29.4006	< 0.0001
TRT (1=Interv., 0=PCB)	-0.3487	0.1579	0.0348
Year	-0.1077	0.0147	< 0.0001
<i>After accounting for confounding factors</i>			
Intercept	224.2987	19.5678	< 0.0001
TRT (1=Interv., 0=PCB)	-0.3318	0.1065	0.0043
Year	-0.1116	0.0098	< 0.0001
Histology			< 0.0001
Bladder vs. renal cell carcinoma	-0.0220	0.6446	0.9730
Breast vs. renal cell carcinoma	-0.8485	0.3244	0.0144
Lung (other solid tumors) vs. renal cell carcinoma	-0.2156	0.3446	0.5369
Prostate vs. renal cell carcinoma	-1.1920	0.3376	0.0015

TRT indicates treatment group of intervention or placebo (1 or 0).
Interv.: Intervention.
PCB: Placebo.

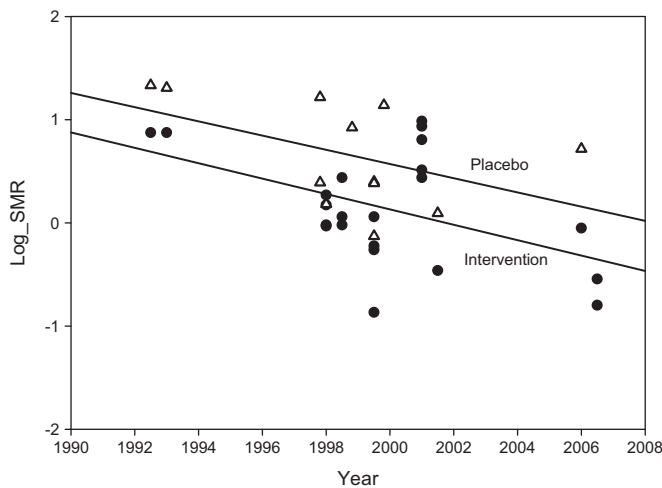


Fig. 4. Comparison of SMR trends for all intervention arms (solid circle) against all placebo arms (open triangle).

on chemotherapy, and percentage of patients with previous SREs (Table 3).

3.2. Analysis of SMR accounting for confounding factors

In patients treated with placebo, after accounting for the confounding factor of histology a significant average decrease in SMR over time is seen. The trend was found to still be statistically significant ($p=0.0011$) with a Pearson’s correlation coefficient of 0.9040. The confounding factor of histology was also found to be insignificant ($p=0.056$). The R^2 for the model was also calculated to be 0.90.

Similarly, when the confounding factors of histology and drug mechanisms were accounted for as confounders, the results indicate there is a significant average SMR decrease over the year in patients receiving interventions ($p=0.0014$). The R^2 for the model was also calculated to be 0.93. The confounding factor of histology was statistically significant ($p=0.0006$), but the drug mechanism was not ($p=0.0698$).

While previously the trend for zoledronic acid trials was not found to be statistically significant, after accounting for differences in histology, the results indicate there is a significant average SMR decrease over time in patients receiving zoledronic acid ($p=0.0211$). The Pearson’s correlation coefficient was found to be 0.8224 for the model. When analyzing the time trend for zoledronic acid trials, the

confounding factor of histology was significant ($p=0.0114$). The R^2 for the model was also calculated to be 0.82.

Finally, after accounting for histology, all patients exhibit significant decreases in SMR over time ($p < 0.0001$). There was also a significant difference between patients treated with intervention or with placebo ($p=0.0043$) (Table 2). The negative coefficient of treatment (-0.3318) indicated patients treated with placebo have higher SMRs compared to patients within intervention arms. The confounding factor of histology is significant ($p < 0.0001$). The R^2 for the model was also calculated to be 0.90. Therefore, after adjusting for confounding histology we still find a significant decreasing time trend and significant treatment effect from intervention.

4. Discussion

This analysis finds a reduction in the occurrence of SMRs over the time frame from 1990 to 2007. SMRs of both placebo and intervention arms decreased over time, but remained relatively constant in patients receiving the third generation bisphosphonate zoledronic acid. In studies with the most recent bone targeted agent denosumab, an additional relative reduction in SMR of 22% was seen in comparison to zoledronic acid [7]. This suggests not only that newer bisphosphonates and bone-targeted agents are improving outcomes for patients, but management strategies and awareness of such disease is improving at the same time.

As is evident by analysis of SMR, improvements are being made in the treatment of bone metastases. This is likely by reducing osteoclast-mediated bone resorption and subsequently normalizing calcium levels. Bisphosphonates have been developed through three generations, with current research focusing on the monoclonal antibody denosumab. Although few direct comparisons were found, second generation bisphosphonates were shown to decrease the risk of SRE similarly to first generation bisphosphonates but with longer lasting pain relief [3]. This can be exemplified by how significantly better bone-pain scores were reported with 90 mg intravenous pamidronate compared with a 1600 mg/day oral clodronate regimen, in patients with bone metastases from a variety of primary sites [8]. In a number of later trials, zoledronic acid has been shown to decrease the number of SREs in comparison to earlier bisphosphonates. As Rosen et al. found, long-term treatment in lung cancer patients and other patients with solid tumor using zoledronic acid (4 mg) has shown an additional 20% reduction in the risk of skeletal complications in comparison to treatment by pamidronate [9].

Table 3
Study design of studies including SMR values or pure SRE numbers.

Authors	Pub year	Total (ITT)	Patient selection	Primary end point	Arm 1	Arm 2	Arm 3	Study duration	% on chemo			% prev SRE		
Dearnaley [31]	2009	819	Prostate	Symptomatic BPFS	Clodronate	Placebo	NA	5 years	NR	NR	NA	NR	NR	NA
Lipton [23]	2004	74	Renal cell carcinoma	Proportion of SRE	Zoledronic acid	Placebo	NA	9 months	NR	NR	NA	82	95	NA
Saad [32]	2004	122	Prostate	Proportion with SRE	Zoledronic acid (4 mg)	Placebo	Zoledronic acid (8/4 mg)	15 months	NR	NR	NR	82	82	NR
Saad [2]	2007	422	Prostate	Proportion with SRE	Zoledronic acid	Placebo	NA	15 months	NR	NR	NA	30.8	37.5	NA
Tripathy [26]	2005	312	Breast	SMR	Ibandronate	Placebo	NA	96 weeks	NR	NR	NA	NR	NR	NA
Rosen [33]	2001	1648	Breast/MM	Non-inferiority, proportion of SRE	Zoledronic acid	Pamidronate	NA	13 months	81	82	NA	68	68	NA
Rosen [21]	2004	1648	Breast/MM—long term	Proportion on SRE	Zoledronic acid	Pamidronate	NA	25 months	NR	NR	NA	NR	NR	NA
Fizazi [10]	2011	1904	Prostate	Time to first on-study SRE	Denosumab	Zoledronic acid	NA	NR	14	14	NA	24	24	NA
Hortobagyi [34]	1996	382	Breast	Proportion with SRE	Pamidronate	Placebo	NA	12 months	100	100	NA	38	47	NA
Kohnno [29]	2005	228	Breast	SRE rate	Zoledronic acid	Placebo	NA	12 months	26	34	NA	34	42	NA
Lipton [4]	2000	754	Breast	SMR	Pamidronate	Placebo	NA	24 months	8.7	11.7	NA	NR	NR	NA
Lipton [24]	2003	74	Renal cell carcinoma	Proportion of SRE	Zoledronic acid	Zoledronic acid	Placebo	9 months	NR	NR	NR	82	81	95
Rosen [25]	2004	773	Lung, other solid tumours	Proportion with SRE	Zoledronic acid (4 mg)	Zoledronic Acid (8 mg)	Placebo	9 months	82	80	80	65	68	73
Rosen [9]	2003	1130	Breast	Proportion with SRE	Zoledronic acid	Zoledronic Acid	Pamidronate	12 months	47	47	47	38	43	37
Saad [20]	2002	643	Prostate	Proportion with SRE	Zoledronic acid (4 mg)	Zoledronic Acid (8 mg)	Placebo	15 months	NR	NR	NR	30.8	32.1	37.5
Saad [28]	2005	422	Prostate	Proportion with SRE	Zoledronic acid	Placebo	NA	15 months	NR	NR	NA	31%	37.5	NA
Saad BJU (RENAL SUBGROUP) [27]	2006	46	Renal cell carcinoma	Proportion with SRE	Zoledronic acid	Placebo	NA	15 months	NR	NR	NA	81	95	NA
Saad BJU (PROSTATE SUBGROUP) [28]	2005	422	Prostate	Proportion with SRE	Zoledronic acid	Placebo	NA	15 months	NR	NR	NA	30.8	37.5	NA
Saad [35]	2010	422	Prostate	Proportion with SRE	Zoledronic acid	Placebo	NA	15 months	NR	NR	NA	30.8	37.5	NA
Small [36]	2003	378	Prostate	Reduction of pain, proportion on SRE	Pamidronate	Placebo	NA	27 weeks	40	43	NA	52	51	NA
Stopeck [7]	2010	2049	Breast	Time to first trial SRE	Denosumab	Zoledronic acid	NA	NR	40	40	NA	37	37	NA
Theriault[3]	1999	372	Breast	SMR	Pamidronate	Placebo	NA	96 weeks	NR	NR	NA	NR	NR	NA
Tripathy [26]	2004	435	Breast	SMR	Ibandronate 20 mg	Ibandronate 50 mg	Placebo	96 weeks	34.7	39.2	32.2	NR	NR	NR
Zaghloul [30]	2010	40	Bladder	Proportion of SRE	Zoledronic acid	Placebo	NA	6 months	NR	NR	NA	NR	NR	NA

ITT: intent to treat population.

Recently, as indicated by Stopeck et al. [7], denosumab significantly delayed the time to first trial SRE and reduced the risk of subsequent SREs when compared to zoledronic acid in breast cancer patients. In a separate trial, Fizazi et al. [10] accrued similar findings with prostate cancer patients, with the median time to first SRE being 20.7 months compared to 17.1 monthly, for denosumab and zoledronic acid, respectively.

The exhibited efficacies of bone targeting treatments, in phase III clinical trials, suggest significant progress in delaying skeletal-related events, with improvements having been seen in the direct comparisons between generations of drugs. These findings also lend clear support to the utility of bone targeted agents in comparison to treatment with placebo. An analysis of phase III trials attests to zoledronic acid's increased benefits over previous generations of bisphosphonates. For this reason, it is the only bisphosphonate that has received US and European approval for treatment of bone metastases, independent of primary tumor type [6].

As treatment intent for patients with advanced cancer is to improve quality of life, it is important to consider the potential

burden of debilitating SREs. Previous studies have found that after SREs, significant decline not limited to physical well-being, but also emotional and functional well-being is seen [11]. In addition, negative financial impact is also observed in patients who have an SRE; the estimated SRE-related cost per patient is USD 11,979 in one's lifetime [11]. This cost, in addition to subsequent supportive care, totals approximately USD 28,000 per patient [12]. Of this, radiotherapy accounted for the greatest proportion of cost (61%) by SRE type, followed by bone surgery (21%) [11]. It is important to note that approximately 80% of the costs of treatment of SREs are incurred within 2 months of the first SRE-related claim. Therefore, proper management with bone targeted therapies are highly relevant in this population, and our study adds to growing evidence supporting the importance of therapy to help prevent or delay bone resorption.

The fact that the SMR decreased in placebo arms over time hints that management of patients with bone metastases and awareness of the risk of SREs has improved. It is possible that, over time, due to improved understanding of bone biology, recognition of early

symptoms of bone metastases, initiation of an improving selection of anti-cancer therapeutic options, early introduction of treatment and better skeletal care education, SRE incidence has declined and will continue to do so over time. In the past decade, improvements have been made to allow for early detection of spinal cord compression; magnetic resonance imaging (MRI) has been demonstrated to be the most reliable method, with 95% diagnostic accuracy [13]. Prophylactic stabilization and the use of prophylactic surgery for metastatic lesions have also been shown to provide a distinct survival advantage and are associated with relatively low perioperative risk [14]. These improvements in management could be reflected in the SMR decrease in the placebo arms over time. In a study of immediate or delayed treatment with zoledronic acid, immediate-start zoledronic acid was found to increase the prevention of bone loss, a factor that can contribute to SREs such as pain and fractures [15]. These results demonstrate the effect of timely treatment that could similarly be revealed in SMR data. A similar effect can be seen with denosumab studies, where better hazard ratio is seen among patients with no prior SRE, compared to those with prior SREs [16]; this indicates increased prevention ability with timely treatment. No data was collected with respect to the date of diagnosis or metastasis of patients, making it difficult to determine the state of the disease at which the patients were referred. But, perhaps this amelioration in management strategies in the latter time period, concurrent with increased bisphosphonate efficacy, could elucidate our SMR trend.

It is also possible that primary therapies directed at the tumour might have had an effect on the time trend results. While the primary therapy practice has not changed; the proportion of patients receiving it has. For example, since the introduction of docetaxel in prostate cancer, across the studies, up to 82% of patients were on chemotherapy. In comparison, in a contemporary trial with the RANKL inhibitor denosumab performed by Fizazi et al. [10], the benefits of bone targeted agents were seen while one third of patients received docetaxel. It can also be seen that in the later studies examined 40% of breast cancer patients had been placed on chemotherapy [7]. While data on whether patients were on chemotherapy was limited, these discrepancies could account for the SMR trend. The proportion of patients on chemotherapy may also reflect a change in the need for primary therapy or changes in patient options. This change in chemotherapy use could account for the trends in SMR rates in the placebo arms of the studies.

The potential improvement in management of patients can be evidenced by a paper comparing baseline symptom severity over two time frames by Khan et al. [17]. Baseline Edmonton Symptom Assessment System (ESAS) scores reported by patients seen from 2006 to 2009 were found to exhibit significant improvement for most items, as compared to values taken from 1999 to 2002. The largest magnitude of difference in symptom severity was found in depression, with a median score for depression of 0.0 from 2006 to 2009 compared to 2.0 from 1999 to 2002 [17]. Similar decreases were also seen in pain, fatigue and sense of wellbeing. A probable cause for these items may be the increased referral to palliative care. An increased trend in palliative care has been exhibited and may significantly reduce the symptom severity of patients at risk of bone metastases, especially when coupled with the aforementioned early incorporation in disease trajectory [18]. It is for this reason, palliative treatment has gained increasing support as a vital component of comprehensive cancer care, with ASCO resolving to induct palliative care as routine by 2020 [19].

The heterogeneity in reporting SRE outcomes limits the comparison of studies using bone targeted agents. More phase III data are available than what have been presented herein (Table 3). Unfortunately, due to varying endpoint definitions in the literature, we are unable to include additional studies which may have strengthened our findings. Heterogeneity may also arise from the differences in

histology between primary breast, prostate, myeloma, lung, renal and bladder cancers, however our results indicate that regardless of history or the different drug mechanisms SMR values are decreasing significantly. Our findings may further be confounded by the variability of the included studies themselves. Certain studies reported extended follow-up periods, while others were published after a predetermined endpoint. Depending on the time frame in which data were captured, this may inflate or deflate true SMR rates. As observed in the data presented, studies on patients with primary renal cell carcinoma generally reported greater SMRs than other cancers, which may have influenced our findings.

Nevertheless, we have included a selection of articles spanning over a decade and a half which clearly demonstrates SMR time trends across generations of bone modifying agents and their respective effects on bone modeling and tumor burden. Our study reflects the trends of the SREs reported in clinical trials, which may not be the same as in daily practice. We encourage clinicians and researchers to report the latter for comparison.

In conclusion, improvements in SMRs of both placebo arms and intervention arms were seen over the years accounting for confounding factors of histology and differences in drugs used. This suggests that newer bisphosphonates and bone-targeted therapies are improving outcomes for patients, adding to the growing evidence in support of bone-targeted agent use. As well, these findings lend clear support to how improvements in management strategies and awareness of bone disease in metastatic cancer parallels the advances made in bone targeting treatments, as evidenced by SMR.

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