

## Comparative Efficacy of Bisphosphonates in Metastatic Breast and Prostate Cancer and Multiple Myeloma: A Mixed-Treatment Meta-analysis

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### Abstract

**Purpose:** A mixed-treatment comparison (MTC) was undertaken to compare the efficacy of zoledronic acid, clodronate, pamidronate, and ibandronate (i.v. and oral) in patients with skeletal-related events (SRE) secondary to metastatic breast and prostate cancer and multiple myeloma.

**Experimental Design:** Studies of bisphosphonates in the three malignancies were identified and SRE data were extracted. Outcomes from the MTC were expressed as the annual SRE rate and as the mean likelihood (probability) ratio for the rate of SREs during treatment with zoledronic acid compared with the other bisphosphonates.

**Results:** A total of 17 studies were identified (7 breast, 3 prostate, and 7 multiple myeloma). Data were available for all bisphosphonates in breast cancer; no data were available for ibandronate (oral or i.v.) in prostate cancer or for oral ibandronate in multiple myeloma. The SRE rates in breast cancer were 1.60 for zoledronic acid, 1.67 for oral ibandronate (excess SRE rate, 4%), 1.70 for i.v. ibandronate (6%), 2.07 for pamidronate (29%), and 2.29 for clodronate (42%). In prostate cancer, the SRE rates were 0.83 for zoledronic acid, 1.11 for clodronate (35%), and 1.41 for pamidronate (71%). In multiple myeloma, the SRE rates were 1.43 for zoledronic acid, 1.64 for pamidronate (15%), 1.90 for clodronate (33%), and 2.49 for i.v. ibandronate (75%).

**Conclusions:** Zoledronic acid seems to be the most efficacious bisphosphonate for reducing the risk of SREs in patients with cancer of the breast or prostate and those with multiple myeloma. *Clin Cancer Res*; 19(24); 6863–72. ©2013 AACR.

### Introduction

The skeleton is a common site of metastatic spread in malignancies, occurring in approximately 65% to 75% of patients with breast and prostate cancer (1, 2), and, inherently, in all patients with multiple myeloma (3). Skeletal complications arising from bone metastases, so-called skeletal-related events (SRE), are associated with significant morbidity and include severe pain requiring palliative radiation therapy or surgery to bone, hypercalcemia of malignancy (HCM), pathologic fractures, and spinal cord compression (1, 2). Functional impairment, loss of mobility, a rapid deterioration in patients' quality of life, and, potentially, reduced survival are

all issues associated with bone metastasis (4, 5). Moreover, patients with cancer have been shown to use progressively more hospital resources and incur increased costs when they develop bone metastases and subsequent SREs (6, 7).

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption (8–10), and a number of amino- and nonaminobisphosphonates are available to oncologists (11), including i.v. preparations of zoledronic acid, pamidronate, and ibandronate and oral formulations of ibandronate and clodronate. As a class, bisphosphonates have been shown, in Cochrane meta-analyses, to be effective for the treatment and prevention of SREs and/or bone pain in advanced breast cancer (12), multiple myeloma (13), and prostate cancer (14). The Cochrane Collaboration has also shown the receptor activator of nuclear factor  $\kappa$ B (RANK) ligand inhibitor, denosumab, to be an effective bone-targeted therapy (12). Few studies, however, have directly compared the individual bisphosphonates.

In breast cancer, zoledronic acid has been shown to be more effective than pamidronate (15). In addition, the investigators in the recently published first results from the Zoledronate versus Ibandronate Comparative Evaluation (ZICE) trial (16) reported that oral ibandronate was inferior to zoledronic acid in terms of the primary endpoint of the SRE rate, although both drugs were similar in delaying the time to first SRE. Head-to-head studies in multiple myeloma

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have also shown zoledronic acid to be at least as effective as pamidronate (15) and more effective than clodronate (17). Currently, no comparative studies of bisphosphonates have been undertaken in prostate cancer, and ibandronate, pamidronate, and clodronate have not been directly compared in any malignancy. Indirect evidence suggests that zoledronic acid and ibandronate might be similarly active at reducing bone turnover markers in patients with breast and non-small cell lung cancer (18, 19), whereas preclinical studies indicate that zoledronic acid is more than 16,000 times more potent than clodronate, 850 times more potent than pamidronate, and 20 times more potent than ibandronate (20).

The limited comparative data available makes definitive differentiation of the efficacy of the individual bisphosphonates difficult. Indeed, national guidelines, such as those from the National Institute for Health and Care Excellence (NICE), often suggest that the choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference, and should be limited to preparations licensed for the particular indication (21). Because it is unlikely that there will be any further head-to-head studies undertaken, it would be useful to investigate other methods of providing quantitative data on the relative effectiveness of the individual bisphosphonates as an aid to clinical decision making.

One approach to evaluating the efficacy of one therapy over another, within the same therapy class, is through the use of a mixed-treatment comparison (MTC). MTCs are an increasingly popular form of meta-analysis that use Bayesian statistics to estimate the comparative effectiveness of multiple treatments using an evidence-based network that combines information from multiple trials that do not compare all treatment options individually, but can be linked by a common comparator (e.g., placebo; refs. 22, 23). Therefore, the MTC approach has the advantage that it can use data from a wider variety of sources than a traditional frequentist meta-analysis (e.g., using risk ratios) and provide (indirectly) information about the comparative effectiveness of drugs in patient populations in which there are no head-to-head studies, which is not possible using a frequentist approach. MTCs are increasingly being used to provide insight into the comparative merits of different therapies in the absence of head-to-head studies and are recognized and recommended by NICE for use in their technology appraisals where direct comparison is lacking (24). The MTC approach has also been adopted by the Cochrane Collaboration in a number of recent systematic reviews (25, 26), although not in the comparisons of bisphosphonates (12–14).

We undertook a MTC meta-analysis to investigate and compare the efficacy of zoledronic acid, clodronate, pamidronate, and ibandronate (i.v. and oral). Because most data for bisphosphonates come from trials in breast cancer, prostate cancer, and multiple myeloma, the MTC was limited to these three malignancies. Although it is recognized that the RANK ligand inhibitor, denosumab, has provided an additional option for the prevention of SREs

in patients with bone metastases secondary to breast, prostate, and other solid tumors (27–30), the focus of this review was to provide further comparative information on the individual bisphosphonates.

## Materials and Methods

### Literature search and selection of studies

The PubMed database was searched to identify all clinical studies that compared a bisphosphonate with either placebo or another bisphosphonate in the treatment and/or prevention of SREs secondary to metastatic breast cancer, prostate cancer, or multiple myeloma. The search included the terms "bisphosphonate," "clodronate," "ibandronate," "ibandronic acid," "pamidronate," "zoledronic acid," "zoledronate," "breast cancer," "prostate cancer," or "multiple myeloma" in the title or abstract, and was limited by "clinical trials, meta-analysis, randomized controlled trial, review" published in English between 1980 and December 2012. This search was supplemented by manual searching of bibliographies of short-listed articles. The inclusion criteria for the MTC were randomized controlled trials (RCT) investigating the efficacy of clodronate, ibandronate, pamidronate, and/or zoledronic acid in breast cancer and prostate cancer metastatic to bone, or multiple myeloma that reported an efficacy endpoint in terms of SREs.

### Data extraction

For each study included in the MTC, baseline data were extracted covering patient demographics, disease characteristics, and how SREs were defined and recorded. Where available, the efficacy endpoint of the annual incidence rate of SREs (events per patient per year) was extracted from the publication. If SRE rates were not directly available, patient incident rates (number of patients affected by SREs per period) were used. In all analyses, SRE rates including HCM, where recorded, were used.

### Data homogeneity

A test of variance, within each cancer type, was undertaken to confirm that there was no *de facto* reason not to include the studies in an MTC. It was determined whether combining the studies within a cancer type produced a tighter variance [expressed as a 95% confidence interval (95% CI)] than the individual study with the lowest variance. If combining the studies produced a tighter variance than from any individual study, it was assumed that the data were suitably homogeneous for inclusion in a MTC.

### MTC meta-analysis

MTC meta-analysis, which uses Bayesian statistics, is distinct from traditional ("frequentist") methods (e.g., risk ratios), having different underlying principles and assumptions, and providing a distinctly different output. An MTC uses a methodology for analyzing the probability of differential performance between treatments, whereas frequentist approaches provide a probability (*P* value) of whether the performances of treatments are the same or not. As such, the results of an MTC are not expressed as a *P* value,

although they can be considered similar/analogous. It can also be argued that, for comparison purposes, the likelihood or probability measured by MTC gives a more practical estimate of relative treatment performance than a traditional *P* value. Some advantages of the Bayesian MTC approach include the following:

- All uncertainty in parameter estimation is included in the final inference;
- Estimation (particularly the uncertainty) for any function of the parameters can be easily obtained by examining the corresponding posterior distribution;
- Prior probabilities are implicit in the methodology;
- Does not rely on large-sample, asymptotic theory, and, therefore, can justifiably use smaller samples.

The MTC was performed using placebo or the control arm as the common comparator. The primary output from the MTC was the annual incidence rate of SREs for each bisphosphonate and placebo within each malignancy. Outcomes were also expressed as the mean likelihood (probability) ratio for the rate of SREs during treatment with the comparator agent (placebo or bisphosphonate) compared with the rate during treatment with zoledronic acid. A positive percentage equated to an excess SRE rate compared with zoledronic acid, whereas a negative percentage equated to a reduced SRE rate compared with zoledronic acid.

All analyses were performed using WinBUGS (Bayesian inference Using Gibbs Sampling) 1.4.3 statistical software (31, 32). This software package uses Markov Chain Monte Carlo modeling, which can be configured to combine and evaluate relative event rates from disparate sources. Algorithms based upon a fixed effects model excluding confounding factors specific to data source were developed in WinBUGS code and used for all the analyses. These algorithms were developed on the assumption of binomial prior and posterior distributions and using *P* (incidence) and *n* (sample size) prior hyperparameters derived from the source publications. When performing the MTC, a 1,000 iteration "burn in" was carried out for each comparison (to enable the software to converge onto a stable model), followed by 10,000 iterations to create the samples for probability estimation.

## Results

### Overview of studies

A total of 17 publications covering 20 RCTs were identified for inclusion in the MTC for the three malignancies (Tables 1–3). With the exception of three studies comparing bisphosphonates [zoledronic acid vs. pamidronate (15) and oral ibandronate (16) in breast cancer and zoledronic acid versus clodronate (17) in multiple myeloma], all studies compared a bisphosphonate with placebo. In total, seven studies investigated zoledronic acid (4 mg every 3–4 weeks, i.v.; refs. 15–17, 33–36), five pamidronate (60/90 mg every 3–4 weeks, i.v.; refs. 15, 37–40), four clodronate (1,600–2,400 mg daily, orally; refs. 17, 41–43), two i.v.

ibandronate (6 mg every 3–4 weeks; refs. 44, 45), and two oral ibandronate (50 mg daily; refs. 16, 46). Of the 14 placebo-controlled studies, 13 showed that bisphosphonates were efficacious in reducing the incidence of SREs in breast cancer, prostate cancer and multiple myeloma; Small and colleagues (38) did not demonstrate any advantage for pamidronate over placebo in preventing SREs in prostate cancer [patients affected by SREs: 42/169 (24.9%) vs. 46/181 (25.4%), respectively; not significant].

### Breast cancer

Seven studies in breast cancer were included in the analysis, including comparisons of zoledronic acid (36), pamidronate (37), clodronate (41), i.v. ibandronate (44) and oral ibandronate (46) with placebo, and zoledronic acid with pamidronate (15) and oral ibandronate (ref. 16; Tables 1 and 4). The 95% CIs for the individual studies ranged from 0.077 to 0.183, which tightened to 0.057 when they were combined, indicating that the studies could be included in a MTC.

Zoledronic acid was associated with the lowest annual incidence rate of SREs (1.60) of the bisphosphonates included in the analysis, followed by ibandronate (oral, 1.67; i.v., 1.70), pamidronate (2.07), and clodronate (2.29; Table 5). This was reflected in the excess SRE rates for clodronate, pamidronate, and i.v. and oral ibandronate over zoledronic acid, which were 42%, 29%, 6%, and 4%, respectively. Because the study by Kohno and colleagues (36) of zoledronic acid versus placebo had a lower SRE rate than the other placebo-controlled studies (1.1 vs. 1.4–4.0, respectively; Table 4) and was undertaken in an Asian rather than predominantly Western population, analyses were also performed with this study excluded. Removing the Kohno study (36) from the analysis resulted in a lower SRE rate for zoledronic acid (1.53 vs. 1.60 with Kohno), with the rate for the other bisphosphonates increasing (oral ibandronate, 1.87 vs. 1.67; i.v. ibandronate, 1.98 vs. 1.70; pamidronate, 2.41 vs. 2.07; clodronate, 2.63 vs. 2.29; Table 5). There was a corresponding increase in the excess SRE rates versus zoledronic acid, ranging from 72% with clodronate to 22% with oral ibandronate.

### Prostate cancer

The three prostate cancer studies included in the analysis compared zoledronic acid (33), pamidronate (38), and clodronate (42) with placebo (Tables 2 and 4); there were no data for ibandronate. Data from the three studies seemed suitably homogeneous for inclusion in an MTC, with the combined variance (95% CI, 0.06) being tighter than for any of the individual studies (95% CI, 0.09–0.13).

The MTC showed that the annual incidence rate of SREs was lowest for zoledronic acid (0.83), followed by clodronate (1.11) and pamidronate (1.41; Table 5). The SRE rate for pamidronate was similar to that for placebo (1.41 vs. 1.47, respectively). Excess SRE rates over zoledronic acid for clodronate and pamidronate were 35% and 71%, respectively.

**Table 1.** Studies of bisphosphonates in breast cancer eligible for inclusion in the MTC meta-analysis

Study	Comparators (regimen)	Patients (n)	Median age (range)	Median time from bone metastases to study entry (mo)	Bone only disease (%)	Prior history of SREs (%)	Included SREs
Rosen et al. (15)	Zoledronic acid (4 mg every 3–4 wks)	377	58	4.4	NR	62	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, hypercalcemia
	Pamidronate (90 mg every 3–4 wks)	389	57	3.6		63	
Barrett-Lee et al. (16)	Zoledronic acid (4 mg every 3–4 wks)	672	NR	NR	NR	NR	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, hypercalcemia
	Oral ibandronate (50 mg daily)	654					
Kohno et al. (36)	Zoledronic acid (4 mg every 3–4 wks)	114	54 <sup>a</sup>	3.9	NR	34	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone <sup>b</sup>
	Placebo	114	54 <sup>a</sup>	3.9	NR	42	
Lipton et al. (37) <sup>c</sup>	Pamidronate (90 mg every 3–4 wks)	367	<50 (25%) 51–65 (42%) >65(33%)	<2 yrs (35.4%) ≥2 yrs (64.6%)	64.3		Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone
	Placebo	384	<50 (29%) 51–65 (38%) >65 (34%)	<2 yrs (35.4%) ≥2 yrs (64.6%)	66.1	Patients with an SRE ≤2 weeks before study were ineligible	
Paterson et al. (41)	Clodronate (1,600 mg daily)	85	58 (26–77)	12 <sup>d</sup>	18	44 <sup>f</sup>	Pathologic fracture, radiotherapy to bone, hypercalcemia
	Placebo	88	61 (33–74)	15 <sup>d</sup>	31 <sup>e</sup>	54 <sup>f</sup>	
Body et al. (44)	i.v. ibandronate (6 mg every 3–4 wks) <sup>g</sup>	154	55	15.4 (mean)	68.8	32 <sup>f</sup>	Pathologic fracture, radiotherapy and surgery to bone
	Placebo	158	56	17.4 (mean)	66.5	29 <sup>f</sup>	
Body et al. (46) <sup>c</sup>	Oral ibandronate (50 mg daily)	287	57 (27–92)	5.5	NR	52 <sup>f</sup>	Pathologic fracture, radiotherapy and surgery to bone
	Placebo	277	56 (26–87)	5.8		43 <sup>f</sup>	

Abbreviation: NR, not reported.

<sup>a</sup>Mean age.<sup>b</sup>Hypercalcemia was recorded but not included in annual incidence rate of SREs.<sup>c</sup>Combined analysis of two RCTs.<sup>d</sup>Median time from any metastases to study entry.<sup>e</sup>Significantly more bone-only disease at baseline in placebo vs. clodronate arm ( $P < 0.05$ ).<sup>f</sup>Prior history of (vertebral) fractures.<sup>g</sup>Trial also includes a 2-mg arm (6 mg is the licensed dose for SREs).

**Table 2.** Studies of bisphosphonates in prostate cancer eligible for inclusion in the MTC meta-analysis

Study	Comparators (regimen)	Patients (n)	Median age (range)	Median time from bone metastases to study entry (mo)	Bone only disease (%)	Prior history of SREs (%)	Included SREs
Saad et al. (33,53)	Zoledronic acid (4 mg every 3 wks)	214	72	16.1	NR	31	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, change of antineoplastic therapy to treat bone pain
Small et al. (38) <sup>a</sup>	Placebo	208	73	17.8	NR	38	
	Pamidronate <sup>b</sup> (90 mg every 3 wks)	169	72	13.2	NR	52	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, change of antineoplastic therapy to treat bone pain, need for a spinal orthotic brace, hypercalcemia
Deamaley et al. (42)	Placebo	181	71	19.2	NR	51	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, change of antineoplastic therapy to treat bone pain, need for a spinal orthotic brace, hypercalcemia
	Clodronate <sup>b</sup> (2,080 mg daily)	155	71 (49–88)	2.5	NR	NR	Symptomatic bone metastases i.e., the need to initiate further treatment
	Placebo	156	71 (47–88)	3.0	NR	NR	

Abbreviation: NR, not reported.

<sup>a</sup>Combined analysis of two RCTs.<sup>b</sup>Not licensed in prostate cancer.

### Multiple myeloma

Seven studies in multiple myeloma were included in the analysis, six of which were placebo controlled: two each for zoledronic acid (34, 35) and pamidronate (39, 40), and one each for clodronate (43) and i.v. ibandronate (ref. 45; Table 3 and 4). One head-to-head comparison of zoledronic acid and clodronate was also included in the analysis (17). The study by Rosen and colleagues (15), which compared zoledronic acid and pamidronate in multiple myeloma and breast cancer, did not report separate results for multiple myeloma, so could not be used in the analysis. Similarly, the Myeloma VI trial (47, 48) of clodronate versus placebo was not included, as the results for overall skeletal morbidity were not in a format suitable for analysis. There were no data available for oral ibandronate in multiple myeloma. The combined 95% CI for the seven studies was 0.08, tighter than for the individual studies (0.14–0.27), indicating that the data could be combined in a MTC.

Zoledronic acid was associated with the lowest SRE incidence rate (1.43) in the MTC, with the comparative rates being 1.64 for pamidronate, 1.90 for clodronate, and 2.49 for i.v. ibandronate (Table 5). The SRE rate for i.v. ibandronate (2.49) was similar to placebo (2.45). Excess SRE rates for pamidronate, clodronate, and i.v. ibandronate over zoledronic acid were 15%, 33%, and 75%, respectively.

### Discussion

Bisphosphonates are an important supportive treatment for many advanced malignancies and, as a class, have demonstrated efficacy in treating or reducing the risk of SREs in advanced breast cancer, multiple myeloma, and prostate cancer (12–14). Evidence-based decision making, however, is complicated by the limited number of head-to-head studies of bisphosphonates. Our MTC involved 17 publications covering 20 RCTs and showed a greater reduction in the annual incidence rate of SREs for zoledronic acid than for the other bisphosphonates in all three malignancies. To our knowledge, this is the first MTC to show differences in SRE risk reduction profiles of currently used bisphosphonates in patients with cancer. In addition, our use of the Bayesian MTC approach has provided, for the first time in a single analysis, an estimation of the effectiveness of the various bisphosphonates relative to each other (via a common comparator), something that would not have been possible with traditional frequentist statistics.

Within the MTC, the excess SRE rates for pamidronate, clodronate, and ibandronate (oral and i.v.) over zoledronic acid ranged from 4% to 42% in breast cancer, 35% to 71% in prostate cancer, and 15% to 75% in multiple myeloma. Exclusion of the study by Kohno and colleagues (36) resulted in greater excess SRE rates for the other bisphosphonates over zoledronic acid in breast cancer, with the remaining studies perhaps more reflective of the clinical situation in Western populations (excess SRE rate minus Kohno, 22%–72%). The apparently increased efficacy of

**Table 3.** Studies of bisphosphonates in multiple myeloma eligible for inclusion in the MTC meta-analysis

Study	Comparators (regimen)	Patients (n)	Median age (range)	Stage (%)	Myeloma subtype (%)	Prior history of SREs (%)	Included SREs
Morgan et al. (17)	Zoledronic acid (4 mg every 3–4 wks) Clodronate (1,600 mg daily)	981	I, 59 (31–74) NI, 73 (69–89)	I, 23; II, 36; III, 31; NA, 10 I, 15; II, 33; III, 41; NA, 12	NR	27 <sup>a</sup> 27 <sup>a</sup> 30 <sup>a</sup> 31 <sup>a</sup>	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, new osteolytic lesion
Avilés et al. (34)	Zoledronic acid (4 mg every 4 wks) Control <sup>h</sup>	46	67 <sup>b</sup> (43–75)	IIa, 100 IIa, 97; IIb, 2	IgG, 62; IgA, 20; light-chain, 11; nonsecretor, 4 IgG, 71; IgA, 20; light-chain, 6; nonsecretor, 3	Presence of ≥1 lytic lesion	New osteolytic lesion, progression of previous bone lesion, pathologic fracture, radiotherapy to bone
Musto et al. (35)	Zoledronic acid (4 mg every 4 wks) Control <sup>h</sup>	81	66 (41–82)	I, 100	IgG, 72; IgA, 28	No evidence of bone disease	Pathologic fracture, new osteolytic lesion, hypercalcemia
Berenson et al. (39)	Pamidronate (90 mg every 4 wks) Placebo	198	64 <sup>b</sup>	I, 100 III, 100	IgG, 74; IgA, 26 IgG, 57; IgA, 14; light-chain, 21; other <sup>c</sup> , 8	Presence of ≥1 lytic lesion	Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, hypercalcemia
Musto et al. (40)	Pamidronate (60 mg every 3–4 wks) <sup>d</sup> Control <sup>h</sup>	45	67 (47–79)	I, 76 II, 24	IgG, 80; IgA, 18; IgD, 2 IgG, 78; IgA, 22; IgD, 0	No bone pain, bone lesions or hypercalcemia	Pathologic fracture, number and progression of osteolytic lesions, hypercalcemia
Lahtinen et al. (43)	Clodronate (2,400 mg daily) Placebo	168	<65, 51% <sup>e</sup> 65–74, 35% >74, 14% <65, 37% 65–74, 45% >74, 18%	NR <sup>f</sup>	NR	0, 53 <sup>a</sup> 1–4, 42 <sup>a</sup> ≥5, 5 <sup>a</sup> 0, 55 <sup>a</sup> 1–4, 39 <sup>a</sup> ≥5, 6 <sup>a</sup>	Pathologic fracture, number and progression of osteolytic lesions
Menssen et al. (45)	i.v. ibandronate <sup>g</sup> (2 mg every 4 wks) Placebo	99	63 <sup>b</sup>	IIa, 18; IIIa, 80 IIa, 15; IIIa, 84	IgG, 54; IgA, 23; light-chain, 15; other <sup>c</sup> , 8 IgG, 57; IgA, 24; light-chain, 17; other <sup>c</sup> , 2	Presence of ≥1 lytic lesion	Pathologic fracture, radiotherapy and surgery to bone, hypercalcemia, significant vertebral reduction (≥25%), severe bone pain (opiate treatment)

Abbreviations: I, intensive; Ig, immunoglobulin; NA, data not available; NI, nonintensive; NR, not reported.

<sup>a</sup>Prior history of (vertebral) fractures.

<sup>b</sup>Mean age.

<sup>c</sup>IgD, IgE, nonsecretor, and unknown.

<sup>d</sup>Licensed dose of pamidronate for multiple myeloma is 90 mg every 3 to 4 weeks.

<sup>e</sup>Patients treated with clodronate were younger ( $P = 0.031$ ).

<sup>f</sup>Newly diagnosed and untreated.

<sup>g</sup>Not licensed in multiple myeloma.

<sup>h</sup>Observation without bisphosphonate.

**Table 4.** Skeletal event rates extracted from source publications in breast cancer, prostate cancer, and multiple myeloma

Study	Comparators	Patients (n)	Annual incidence rate	Patients affected (follow-up duration)
<i>Breast cancer</i>				
Rosen et al. (15)	Zoledronic acid	139	0.91	—
	Pamidronate	140	1.57	—
Barrett-Lee et al. (16)	Zoledronic acid	672	0.42 <sup>a</sup>	—
	Oral ibandronate	654	0.50 <sup>a</sup>	—
Kohno et al. (36)	Zoledronic acid	114	0.63	—
	Placebo	114	1.10	—
Lipton et al. (37)	Pamidronate	367	2.50	—
	Placebo	384	4.00	—
Paterson et al. (41)	Clodronate	85	2.19	—
	Placebo	88	3.05	—
Body et al. (44)	i.v. Ibandronate	154	1.76	—
	Placebo	158	3.34	—
Body et al. (46)	Oral ibandronate	287	0.76	—
	Placebo	277	1.39	—
<i>Prostate cancer</i>				
Saad et al. (33)	Zoledronic acid	214	0.77	—
	Placebo	208	1.47	—
Small et al. (38)	Pamidronate	169	—	42 (27 wks)
	Placebo	181	—	46 (27 wks)
Dearnaley et al. (42)	Clodronate	155	—	94 (median, 236 wks)
	Placebo	156	—	103 (median, 236 wks)
<i>Multiple myeloma</i>				
Morgan et al. (17)	Zoledronic acid	981	0.33	—
	Clodronate	979	0.43	—
Avilés et al. (34)	Zoledronic acid	46	—	10 (median, 198 wks)
	Control	48	—	23 (median, 198 wks)
Musto et al. (35)	Zoledronic acid	81	—	20 (median, 259 wks)
	Control	82	—	29 (median, 259 wks)
Berenson et al. (39)	Pamidronate	198	1.3	—
	Placebo	179	2.2	—
Musto et al. (40)	Pamidronate	45	—	4 (median, 204 wks)
	Control	45	—	9 (median, 204 wks)
Lahtinen et al. (43) <sup>b</sup>	Clodronate	108	—	71 (104 wks)
	Placebo	96	—	83 (104 wks)
Menssen et al. (45)	i.v. ibandronate	99	2.13	—
	Placebo	99	2.05	—

<sup>a</sup>Data estimated from figure in poster.<sup>b</sup>Data taken from the Cochrane review (13).

zoledronic acid over the other bisphosphonates may relate to it having the greatest potency, as observed in preclinical studies (20). Interestingly, however, whereas zoledronic acid remained the most efficacious in all three cancer types, the ranking of the other bisphosphonates varied depending on the malignancy in question. In breast cancer, ibandronate (oral and i.v.) seemed to be the second most efficacious bisphosphonate, followed by pamidronate, then clodronate. In prostate cancer, however, clodronate seemed more effective than pamidronate, which performed little better

than placebo (SRE rate, 1.41 vs. 1.47, respectively). Finally, in multiple myeloma, pamidronate was more efficacious than clodronate, with ibandronate (i.v.) having similar efficacy to placebo (SRE rate, 2.49 vs. 2.45, respectively). Only the results in breast cancer follow the relative potencies seen in preclinical studies (20). It could be hypothesized that the varying efficacy of ibandronate, clodronate, and pamidronate might be due in part to the differing underlying pathologies of the bone metastases from each malignancy: more osteoblastic lesions in prostate cancer,

**Table 5.** Annual incidence rates for each bisphosphonate and placebo and relative (excess) SRE rates compared with zoledronic acid in breast cancer, prostate cancer, and multiple myeloma

Bisphosphonate	Breast cancer <sup>a</sup>		Prostate cancer		Multiple myeloma	
	Excess SRE rate (%)	Annual incidence rate	Excess SRE rate (%)	Annual incidence rate	Excess SRE rate (%)	Annual incidence rate
Zoledronic acid	—	1.60 (1.53)	—	0.83	—	1.43
Clodronate	42 (72)	2.29 (2.63)	35	1.11	33	1.90
Pamidronate	29 (58)	2.07 (2.41)	71	1.41	15	1.64
i.v. Ibandronate	6 (30)	1.70 (1.98)	—	—	75	2.49
Oral ibandronate	4 (22)	1.67 (1.87)	—	—	—	—
Placebo/control	106 (150)	3.30 (3.82)	78	1.47	72	2.45

<sup>a</sup>Values in parentheses are when Kohno et al. study (36) study (zoledronic acid vs. placebo) was removed from the MTC.

more lytic lesions in multiple myeloma, and mixed lesions in breast cancer (2). It could equally be argued, however, that, overall, the breast cancer studies were more comparable in terms of patient populations and skeletal endpoints than was the case for the other two malignancies. The data in prostate cancer were relatively limited and included additional SREs not counted in the breast and myeloma studies (e.g., change of antineoplastic therapy to treat bone pain; refs. 33, 38). All of these considerations could have affected the ordering of bisphosphonates.

Although a mixed-treatment analysis may be argued to make optimal use of the available data from individual studies, several limitations need to be taken into account when interpreting the results. Arguably, the time to first event would have been a stronger endpoint to use; however, as this was not available for all studies, SRE rates can be considered a meaningful common endpoint. Other limitations include variations in the patient populations within each malignancy, particularly in multiple myeloma, in which studies covering early (stage I) and later disease (stage III) were included; differences in skeletal endpoints and SRE definitions and assessment (e.g., employment or not of an SRE "window" preventing double counting of events); the utilization of an observational, non-bisphosphonate treated arm rather than a placebo arm in three of the myeloma studies (34, 35, 40); and the time period across which the studies were undertaken (1992–2012), during which, for example, there has been a marked reduction in the use of radiotherapy in treating patients with bone metastases (especially in multiple myeloma) during the past decade, which would have had a commensurate effect on SRE rates. Although there is acknowledged variability in these factors between studies that may have influenced the MTC to a greater or lesser extent, it is important to remember that the MTC was analyzing the relative differences between treatments in each study, not the absolute rates; hence, this helped to even out any variability in the individual studies. Further support for the validity of the meta-analysis comes from the results of the heterogeneity tests, which showed no

*de facto* reason why the studies in each cancer type could not be combined in an MTC.

Although this analysis provides interesting new evidence about the relative efficacy of the various bisphosphonates in each type of cancer studied, a number of other, often interrelated, factors might influence the choice of bisphosphonate. Local availability, drug and administration costs, clinician familiarity, patient preference, tolerability, and patient adherence/compliance can all influence decision making. The i.v. bisphosphonates have potential advantages over oral bisphosphonates in terms of adherence (49), with persistence of treatment having been linked to better outcomes (50). Intravenous bisphosphonates would also be appropriate in patients with dysphagia or in those who cannot tolerate the gastrointestinal side effects associated with oral bisphosphonate. Oral bisphosphonates, in contrast, might be considered to be more convenient, obviating the requirement for patients to travel to the hospital for infusions and also potentially freeing up clinic capacity. Patients with renal dysfunction might also be more suitable candidates for oral bisphosphonate therapy, due to reductions in renal function associated with i.v. bisphosphonates, although this assertion has recently been challenged, with results from the MRC Myeloma IX trial showing that renal adverse events occur at a similar rate between oral and i.v. bisphosphonates (17). The risk of osteonecrosis of the jaw should also be considered and appropriate steps taken to mitigate this, including consideration of which bisphosphonate to use. The wider health economics can also play a key role in the choice of bisphosphonate, as the funding and/or reimbursement stream may dictate whether an i.v. or oral bisphosphonate or, indeed, whether a switch from one to the other, might be most cost effective in a given locality. The potential for bisphosphonates to improve progression-free and overall survival via suppression of tumor growth and survival, inhibition of tumor-mediated angiogenesis, or stimulation of patients' anticancer immune response, is an area of active research (51) that also might influence the use of these therapies in the future. The availability of the monoclonal antibody



denosumab (52), representing a new generation of bone targeted agents, has further increased the therapeutic options for oncologists in the treatment and prevention of SREs in their patients. Ultimately, choice of therapy should be made on an individual patient basis, taking into consideration all of the earlier factors.

This MTC has provided decision makers with a further useful insight into the efficacy of the different bisphosphonates currently available to prevent or treat SREs. Of the bisphosphonates investigated, zoledronic acid seemed to be the most efficacious for reducing the risk of SREs in all three tumor types studied: breast cancer, prostate cancer, and multiple myeloma.

### Disclosure of Potential Conflicts of Interest

C. Palmieri serves as a consultant/advisory board member for Novartis and Roche Products Limited. J. Brown is a consultant/advisory board member and has received honoraria from Amgen and Novartis. No potential conflicts of interest were disclosed by the other authors.

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