

Systematic Literature Review and Network Meta-Analysis Comparing Bone-Targeted Agents for the Prevention of Skeletal-Related Events in Cancer Patients With Bone Metastasis

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Key Words. Bisphosphonates • Denosumab • Skeletal-related events • Bone metastasis • Network meta-analysis

ABSTRACT

Background. Complications from skeletal-related events (SREs) constitute a challenge in the care of cancer patients with bone metastasis (BM).

Objectives. This study evaluated the comparative effectiveness of pamidronate, ibandronate, zoledronate, and denosumab in reducing the morbidity of SREs in cancer patients with BM.

Methods. Medline (1948 to January 2014), Embase (1980 to January 2014), the Cochrane Library (2014 issue 1), and Web of Science with Conference Proceedings (1970 to January 2014) were searched. Only randomized controlled trials assessing denosumab, bisphosphonates, or placebo in cancer patients with BM were included. The primary outcomes were SREs and SREs by type. The network meta-analysis (NMA) was performed with a random-effects Bayesian model.

Results. The NMA included 14 trials with 10,192 patients. Denosumab was superior to placebo in reducing the risk of SREs (odds ratio [OR]: 0.49; 95% confidence interval [CI]:

0.31–0.75), followed by zoledronate (OR: 0.57; 95% CI: 0.41–0.77) and pamidronate (OR: 0.55; 95% CI: 0.41–0.72). Ibandronate compared with placebo could not reduce the risk of SREs. Denosumab was superior to placebo in reducing the risk of pathologic fractures (OR: 0.50; 95% CI: 0.32–0.79), followed by zoledronate (OR: 0.61; 95% CI: 0.43–0.86). Denosumab was superior to placebo in reducing the risk of radiation (OR: 0.51; 95% CI: 0.35–0.75), followed by pamidronate (OR: 0.67; 95% CI: 0.52–0.86) and zoledronate (OR: 0.70; 95% CI: 0.52–0.96).

Conclusion. This NMA showed that denosumab, zoledronate, and pamidronate were generally effective in preventing SREs in cancer patients with BM. Denosumab and zoledronate were also associated with reductions in the risk of pathologic fractures and radiation compared with placebo. Denosumab was shown to be the most effective of the bone-targeted agents. *The Oncologist* 2015;20:440–449

Implications for Practice: Bone metastasis (BM) can lead to skeletal-related events (SREs), which can dramatically reduce patients' quality of life and even shorten survival. We used network meta-analysis to evaluate the comparative effectiveness of bone-targeted agents (BTAs) in reducing the morbidity of SREs in cancer patients with BM. We found that denosumab, zoledronate, and pamidronate were generally effective (compared with placebo), and denosumab was shown to be the most effective BTA. Reduction in the incidence of pathologic fractures and radiation was the main cause of reduced risk of SREs. The findings of this study highlight the importance of the use of BTAs in cancer patients with BM.

INTRODUCTION

Bone is the most common site of metastasis in cancer, and cancer metastases to the bone are most prevalent among patients with advanced cancer of the breast (73%), prostate (68%), or lung (36%) [1]. Bone metastasis (BM) can lead to skeletal-related events (SREs), defined as pathologic fracture, spinal cord compression, requirement for radiation or surgery to bone, and hypercalcemia [2]. Data from the untreated arms

of clinical trials indicate that SREs are most common in patients with BM secondary to breast cancer (2-year cumulative incidence of 68%), followed by prostate cancer (2-year cumulative incidence of 49%), and non-small cell lung cancer (NSCLC) and other solid tumors (OST; 21-month cumulative incidence of 48%) [3–5]. Observational studies yielded similar patterns, with a 1-year cumulative incidence of SREs after BM

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diagnosis of 46% in prostate cancer patients and 38% in female breast cancer patients [6, 7].

BM and subsequent SREs can be an important burden on a cancer patient's quality of life (QOL) and overall health status [8]. SREs can dramatically reduce patients' QOL and even shorten survival [9]. Treatment of BM includes orthopedic management, radiation, surgery, and systemic treatments (e.g., bone-targeting agents [BTAs], endocrine therapy, chemotherapy).

Currently licensed bisphosphonates include zoledronate (any advanced malignancy involving bone), pamidronate (breast cancer or multiple myeloma), clodronate (breast cancer or multiple myeloma), and ibandronate (breast cancer). Bisphosphonates are administered either intravenously (zoledronate, pamidronate, or ibandronate) or orally (clodronate or ibandronate) and have been associated with renal toxicity [10]. Denosumab (Xgeva; Amgen, Thousand Oaks, CA, <http://www.amgen.com>) is a RANK ligand inhibitor, licensed for the prevention of SREs in BM from solid tumors. It is administered by subcutaneous injection and does not require renal monitoring [11].

When comparing the effectiveness of two or more interventions, randomized clinical trials (RCTs) that compare the interventions directly (head-to-head trials) are often preferred for health technology assessment and reimbursement (HTA) decision making. Three RCTs have evaluated denosumab compared with zoledronate for the prevention of SREs [12–14]. No head-to-head trials have compared denosumab with other bisphosphonates or best supportive care. Such comparisons are important because of the wide variation in practice and HTA decision making. Some centers use only zoledronate, and some use a variety of bisphosphonates, whereas others do not use bisphosphonates at all (especially in cancer other than breast).

Modern statistical techniques, such as network meta-analysis (NMA), can simultaneously analyze direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator (e.g., placebo or some standard treatment) to overcome some of the challenges posed by the paucity of direct evidence [15]. The objective of our research was to evaluate the comparative effectiveness of BTAs including pamidronate, ibandronate, zoledronate, or denosumab in reducing the morbidity of SREs in cancer patients with BM.

MATERIALS AND METHODS

Literature Search and Selection of Studies

Studies were identified by systematic searches of the following databases: Medline (1948 to January 2014), Embase (1980 to January 2014), the Cochrane Library (all sections of 2014 issue 1), and Web of Science with Conference Proceedings (1970 to January 2014). Additional meeting abstracts (2010 to 2014) were identified by searching the American Society of Clinical Oncology, the American Urological Association, and the San Antonio Breast Cancer Symposium. Reference lists of all included studies were scanned to identify additional potentially relevant studies. The titles and abstracts of all papers identified by the search strategy were screened, and full-text copies of all potentially relevant studies were obtained.

The following search strategy was used for Medline: step 1, exp Diphosphonates; step 2, RANK ligand; step 3, (denosumab or bisphosphonate* or ibandron* or pamidron* or zoledron*).tw.; step 4, or/1-3; step 5, exp Neoplasms; step 6, (solid tumor or solid tumor* or cancer or carcinoma).tw.; step 7, or/5-6; step 8, 4 and 7; step 9, exp Bone Neoplasms; step 10, (bone metast*).tw.; step 11, (skeletal or fracture*).tw.; step 12, or/9-11; step 13, 8 and 12; step 14, randomized controlled trial.pt.; step 15, 13 and 14; step 16, limit 15 to the English language. This search strategy was adapted, as appropriate, for the other databases.

Only RCTs evaluating denosumab, pamidronate, ibandronate, zoledronate, or placebo in reduction of SREs overall and by type were included. Screening was performed by two independent authors, and disagreements were resolved by discussion. After piloting a data-extraction form, data were extracted by one author and checked by a second. Data included study characteristics, inclusion and exclusion criteria, and results (SREs overall and by type).

Quality Score

The magnitude and heterogeneity of risk estimates may depend on the methodological quality associated with the underlying study and with the risk-estimate derivation. Similar to previous systematic review [16] of the association between BTAs and SREs, the authors used a quality score proposed by Higgins et al. [17] to assess the methodological quality of the studies and the consistency of the available evidence.

Main Statistical Analysis

The primary analyses were conducted with a Bayesian Markov Chain Monte Carlo method and fitted with the Bayesian software in WinBUGS version 1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, U.K., <http://www.mrc-bsu.cam.ac.uk>) [18], the R2WinBUGS package [19] and GeMTC package in R software (R Foundation, Vienna, Austria, <http://www.r-project.org>) [20], and ADDIS 1.16.5 (drugis.org, Groningen, The Netherlands, <http://drugis.org/software/addis1/index>) [21]. For the analyses in WinBUGS, every sample consisted of 100,000 iterations with an initial burn-in period of 10,000 iterations [22]. The probability of the outcome was modeled with a binomial distribution, and each pair of treatments was compared by estimating the odds ratio (OR) of the outcome. We assumed that each of the log ORs had been sampled from a normal distribution and that treatment effects were wholly exchangeable within studies. Trials with zero cells in both arms or nodes in which there were no events were excluded from the evidence networks because they did not contribute information or allow interpretable information.

We gave vague prior information for all trial baselines, treatment effects, and between-trial variances. The autocorrelation plots showed that throughout the iterative process, the autocorrelation was satisfactorily reduced to a nominal amount, and the Brooks-Gelman-Rubin plots showed that the model had converged satisfactorily [22]. We assessed the fit of our model using the deviance information criterion, a measure of model fit that penalizes model complexity. This criterion advocates selecting the model with the lowest deviance information criterion value among a series of competing models for the same data because this model is believed to provide the best fit to the data [23].

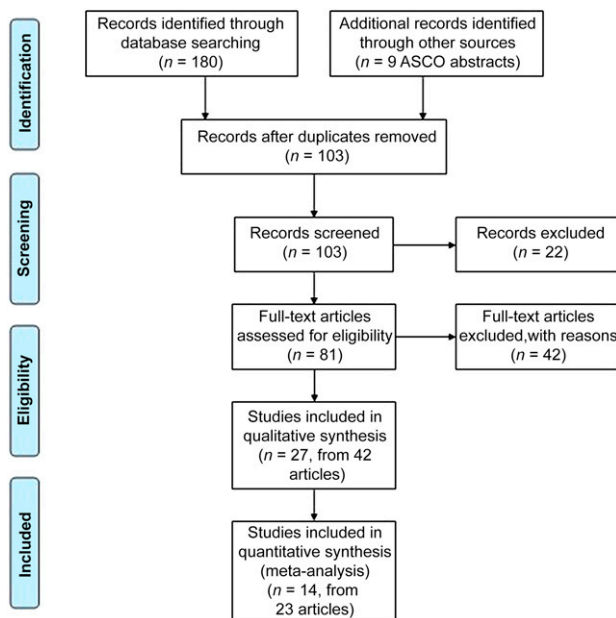


Figure 1. PRISMA flow diagram.

Abbreviation: ASCO, American Society of Clinical Oncology.

All results for the NMA were reported as odds ratio with corresponding 95% credibility intervals (CrIs). Credibility intervals were the Bayesian equivalent of classic confidence intervals (CIs). To ensure consistency, we conducted direct pairwise comparison meta-analysis whenever possible and adjusted indirect comparisons according to the methods described by Bucher et al. [24]. For pairwise meta-analyses, we tested heterogeneity between trials with the I^2 statistic, with $I^2 > 50\%$ indicating significant heterogeneity. A random-effects model (DerSimonian-Laird) was used if significant heterogeneity was detected. To address clinical heterogeneity and the underlying assumption of exchangeability, we performed a meta-regression analysis using Stata 10.1 (StataCorp LP, College Station, TX, <http://www.stata.com>) to see whether a difference in patient population affected the relative treatment effects [25].

RESULTS

Literature Search

The studies were independently assessed for suitability for inclusion in the NMA. Results of the literature search are shown in Figure 1, and 14 studies met the inclusion criteria. The characteristics and results of the 14 studies included in the NMA are shown in Table 1.

Study Characteristics

Nine studies included patients with breast cancer, three included patients with prostate cancer, and two included patients with NSCLC and OST. Three studies compared denosumab with zoledronate, three compared zoledronate with placebo, two compared zoledronate with pamidronate, one compared zoledronate with ibandronate, and four compared pamidronate with placebo.

Twelve studies were international, one study recruited only patients from Japan [34], and one study recruited patients from the U.K. [35]. Patients were youngest in the breast cancer studies and oldest in the prostate cancer studies. The

proportion of patients with a previous SRE at baseline ranged from 24% [12] to 73% [5, 42].

Study Quality

The quality of the studies included in the NMA was high (Table 2). There was a low risk of bias for the majority of categories. Most evidence was of moderate to good quality. Hortobagyi et al. [3, 27] and Berenson et al. [30] failed to describe sequence generation or allocation concealment. Hortobagyi et al. [3, 27], Hultborn et al. [29], and Kohno et al. [34] did not sufficiently address incomplete outcome data. In the study by Conte et al. [26], placebo infusions were not administered to control because of ethical objections in several countries, and the study by Barrett-Lee et al. [35] had an open-label design. Our searches were appropriate, but the possibility of publication bias cannot be excluded; however, it is unclear whether reporting biases would tend to favor any particular treatment.

Reduction in SREs in Cancer Patients With BM

Reduction in SREs Overall

The NMA model converged, and there were no significant inconsistencies between the direct and indirect evidence within the NMA. Three BTAs were associated with significant reductions in SREs overall compared with the placebo in cancer patients with BM. Denosumab was superior to placebo in significantly reducing the risk of SREs (odds ratio [OR]: 0.49; 95% CI: 0.31–0.75), followed by zoledronate (OR: 0.57; 95% CI: 0.41–0.77) and pamidronate (OR: 0.55; 95% CI: 0.41–0.72). Ibandronate compared with placebo could not significantly reduce the risk of SREs overall (Fig. 2). The impact of BTAs in preventing SREs overall and by type (pathologic fractures, radiation, surgery, and spinal cord compression) compared with placebo are depicted in Figure 2.

More extensive results for the relative efficacies of all BTAs are presented in Table 3. For each pairwise comparison of BTAs, the 95% CrIs for ORs were wide and included. The lower-left results in Table 3 presented ORs estimated from direct evidence alone, whereas the upper-right results presented ORs estimated from the NMA. We could not find that one BTA was superior to any other in reducing the risk of SREs.

According to rank probability (Fig. 3), denosumab was the best alternative compared with the other BTAs because it had a much higher score on rank (score of 5), which indicated it had much lower incidence of SREs. In contrast, placebo was the worst, with rank of 1 being the highest and rank of 5 being the lowest for probability. The rank probabilities were summed to 1, both within a rank for all treatments and within a treatment for all ranks.

Reduction in Pathologic Fractures

Denosumab and zoledronate were associated with significant reductions in risk of pathologic fractures compared with placebo. Denosumab was superior to placebo in significantly reducing the risk of pathologic fractures (OR: 0.50; 95% CI: 0.32–0.79), followed by zoledronate (OR: 0.61; 95% CI: 0.43–0.86). No significant reduction in the risk of pathologic fracture events was observed between pamidronate or ibandronate and placebo (Fig. 2; Table 3). Rank probability also showed that denosumab was the best alternative compared with the other BTAs, and zoledronate was the second best (Fig. 3).

Table 1. Characteristics of studies included in the Network Meta-Analysis

Study; duration	Study design	Cancer type	Interventions (n)	Age, median (range) or mean \pm SD	Prior history of SREs, n (%)	Prior history of BTAs	Included SREs
Conte et al. (1996) [26]; until PD	RCT	Breast cancer	Pamidronate 45 mg q3w (143)	58 (30–79)	35 (24.5)	NA	Time to progression; pathologic fractures, surgery, radiation, and hypercalcemia
			Placebo (152)	58 (31–78)	32 (21.1)		
Hortobagyi et al. (1996) [3, 27]; 48 weeks	DB RCT	Breast cancer	Pamidronate 90 mg q4w (185)	57 \pm 12	71 (38)	Naïve	Pathologic fractures (vertebral or nonvertebral), surgery, radiation and hypercalcemia
			Placebo (195)	56 \pm 12	92 (47)		
Theriault et al. (1999) [3, 28]; 2 years	DB RCT	Breast cancer	Pamidronate 90 mg q4w (182)	60 \pm 12	NA	Naïve	SMPR; pathologic fractures (vertebral or nonvertebral), surgery, radiation, spinal cord compression, and hypercalcemia
			Placebo (189)	62 \pm 11			
Hultborn et al. (1999) [29]; 2 years	DB RCT	Breast cancer	Pamidronate 60 mg q4w (201)	60	(43)	Naïve	Pathologic fractures, surgery, radiation, and hypercalcemia
			Placebo (203)	61	(40)		
Berenson et al. (2001) [30]; 10 months	DB RCT	Breast cancer or MM	Zoledronate 4 mg q4w (67)	59.9 \pm 11.3	55 (82)	Naïve	Pathologic fractures, surgery, radiation, spinal cord compression, and hypercalcemia
			Pamidronate 90 mg q4w (73)	57.7 \pm 11.8	59 (81)		
Rosen et al. (2001–2004) [31–33]; 24 months	DB RCT	Breast cancer	Zoledronate 4 mg q3–4w (378)	58	232 (62)	Naïve within 12 months	SMPR; pathologic fractures (vertebral or nonvertebral), surgery, radiation, spinal cord compression, and hypercalcemia
			Pamidronate 90 mg q3–4w (388)	56	244 (63)		
Kohno et al. (2005) [34]; 12 months	DB RCT	Breast cancer	Zoledronate 4 mg q4w (114)	54.3	39 (34.2)	Naïve within 12 months	Pathologic fractures, surgery, radiation, spinal cord compression, and hypercalcemia
			Placebo q4w (113)	53.5	47 (41.6)		
Stopeck et al. (2010) [14]; 34 months	DB RCT	Breast cancer	Denosumab 120 mg q4w (1,026)	57	378 (36.8)	Naïve	Pathologic fractures, surgery, radiation, and spinal cord compression
			Zoledronate 4 mg q4w (1,020)	56	373 (36.6)		
Barrett-Lee et al. (2014) [35]; 96 weeks	RCT	Breast cancer	Ibandronate 50 mg daily (705)	61 (52–70)	298 (42)	Naïve within 6 months	Pathologic fractures, surgery, radiation, spinal cord compression, and hypercalcemia
			Zoledronate 4 mg q3–4w (699)	61 (52–69)	294 (42)		
Saad et al. (2002–2007) [36–40]; 15 months	DB RCT	Prostate cancer	Zoledronate 4 mg q3w (214)	72	66 (30.8)	Naïve	Pathologic fractures (vertebral or nonvertebral), surgery, radiation, and spinal cord compression
			Placebo (208)	73	78 (37.5)		
Small et al. (2003) [41]; 27 weeks	DB RCT	Prostate cancer	Pamidronate 90 mg q3w (185)	72 (46–89)	87 (52)	<3 doses or naïve within 90 days	Pathologic fractures (vertebral or nonvertebral), surgery, radiation, spinal cord compression, and hypercalcemia
			Placebo (195)	71 (42–88)	92 (51)		
Fizazi et al. (2011) [12]; 27 months	DB RCT	Prostate cancer	Denosumab 120 mg q4w (950)	71	232 (24)	Oral bisphosphonate for osteoporosis was allowed	Pathologic fractures, surgery, radiation, and spinal cord compression
			Zoledronate 4 mg q4w (951)	71	231 (24)		
Rosen et al. (2003–2004) [5, 42]; 9 months	DB RCT	NSCLC and OST	Zoledronate 4 mg (254)	64	166 (85)	Naïve within 30 days	Pathologic fractures, surgery, radiation, spinal cord compression, and hypercalcemia
			Placebo (247)	64	179 (73)		
Henry et al. (2010–2011) [13, 43]; 7 months	DB RCT	NSCLC and OST	Denosumab 120 mg q4w (890)	61	446 (50)	Naïve	Pathologic fractures, surgery, radiation, and spinal cord compression
			Zoledronate 4 mg q4w (886)	60	440 (50)		

Abbreviations: DB, double-blind; BTA, bone-targeted agent; MM, multiple myeloma; NA, not available; NSCLC, non-small cell lung cancer; OST, other solid tumors; PD, progressive disease; q3w, every 3 weeks; RCT, randomized controlled trial; SMPR, skeletal morbidity period rate; SRE, skeletal-related event.

Table 2. Risk of bias of studies included in the network meta-analysis

Study	Adequate sequence generation	Adequate allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting
Breast Cancer					
Conte et al. (1996) [26]	Low	Low	High	Low	Low
Hortobagyi et al. (1996) [3, 27]	Low	Low	Low	Unclear	Low
Hultborn et al. (1999) [29]	Low	Low	Low	Unclear	Low
Theriault et al. (1999) [3, 28]	Unclear	Unclear	Low	Low	Low
Berenson et al. (2001) [30]	Unclear	Unclear	Low	Low	Low
Kohnno et al. (2005) [34]	Low	Low	Low	Unclear	Low
Rosen et al. (2001–2004) [31–33]	Low	Low	Low	Low	Low
Stopeck et al. (2010) [14]	Low	Low	Low	Low	Low
Barrett-Lee et al. (2014) [35]	Low	Low	High	Low	Low
Prostate Cancer					
Saad et al. (2002–2007) [36–40]	Low	Low	Low	Low	Low
Small et al. (2003) [41]	Low	Low	Low	Low	Low
Fizazi et al. (2011) [12]	Low	Low	Low	Low	Low
NSCLC and OST					
Rosen et al. (2003–2004) [5, 42]	Low	Low	Low	Low	Low
Henry et al. (2010–2011) [13, 43]	Low	Low	Low	Low	Low

Abbreviations: NSCLC, non-small cell lung cancer; OST, other solid tumors.

Reduction in Radiation to Bone

Denosumab, zoledronate, and pamidronate were associated with significant reductions in risk of the need for radiation compared with placebo. Denosumab was superior to placebo in significantly reducing the risk of the need for radiation (OR: 0.51; 95% CI: 0.35–0.75), followed by pamidronate (OR: 0.67; 95% CI: 0.52–0.86) and zoledronate (OR: 0.70; 95% CI: 0.52–0.96). No significant reduction in the risk of the need for radiation was observed between ibandronate and placebo (Fig. 2; Table 3). Rank probability also showed denosumab was the best therapy compared with the other BTAs, and pamidronate was the second most effective therapy (Fig. 3).

Reduction in Bone Surgery

Only pamidronate was superior to placebo in significantly reducing the risk of bone surgery (OR: 0.60; 95% CI: 0.37–0.98), and thus the probability demonstrated that pamidronate was the best alternative. In contrast, denosumab, zoledronate, and ibandronate were not associated with significant reductions in the risk of surgery compared with placebo (Fig. 2, 3).

Reduction in Spinal Cord Compression

None of the four BTAs were associated with significant reductions in the risk of spinal cord compression versus placebo (Fig. 2).

Direct SRE Results in Breast Cancer Patients With BM

Similarly, denosumab was superior to placebo in significantly reducing the risk of SREs overall (OR: 0.33; 95% CI: 0.15–0.73), followed by zoledronate (OR: 0.43; 95% CI: 0.26–0.70) and pamidronate (OR: 0.45; 95% CI: 0.29–0.62). Ibandronate compared with placebo could not significantly reduce the risk of SREs (Fig. 4).

Denosumab and pamidronate were associated with significant reduction of both pathologic fractures and the need for radiation compared with placebo in breast cancer

patients with BM. The effect of zoledronate was limited to significantly reducing the risk of pathologic fractures in breast cancer patients with BM. No significant reduction in the risk of surgery or spinal cord compression was observed for BTAs compared with placebo.

DISCUSSION

In this study, we performed an NMA to compare the efficacy of available BTAs for the prevention of SREs in cancer patients with BM. Denosumab, zoledronate, and pamidronate showed statistically significant efficacy compared with placebo. Denosumab demonstrated the highest probability of being the most efficacious treatment of all therapies analyzed. The evidence of the efficacy of these drugs in reducing the risks of SREs was related mainly to the reduction in the incidence of pathologic fractures and the need for radiation.

Strengths of the Study

Undertaking an NMA allows for estimation of effectiveness of therapies when no direct data comparison is available. This was the case for comparing placebo with pamidronate, ibandronate, zoledronate, and denosumab. NMAs provide a valid statistical alternative to direct head-to-head studies [18, 44]. An advantage of Bayesian NMAs, such as this study, over frequentist approaches is the ability to rank treatments according to the probability of being the best (i.e., most effective), which could be useful for clinical therapy decisions and HTA decision making [45–47].

A comprehensive and robust search strategy was used. Rigorous inclusion and exclusion criteria were used and included only high-quality evidence (RCTs). Not all studies identified in the Cochrane Review were included in our NMA because of our stricter inclusion criteria. We included, for example, only studies that evaluated the efficacy in reduction of SREs overall and by type; this excluded three studies that

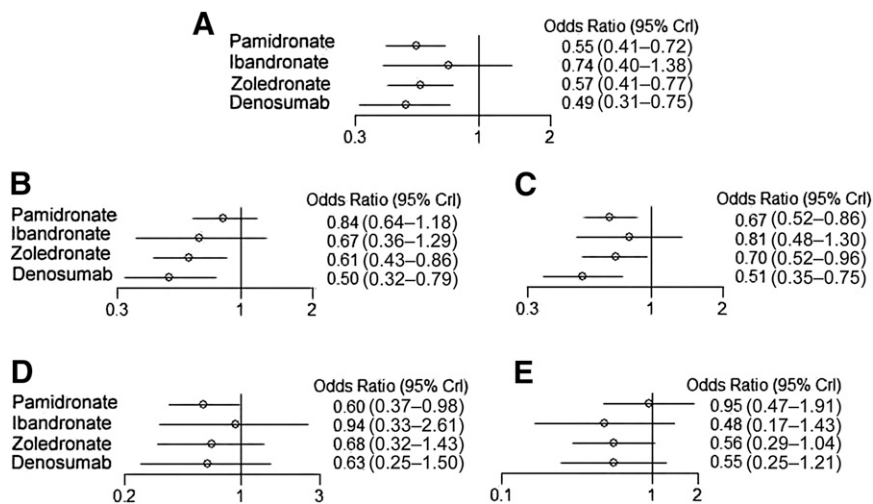


Figure 2. Odds ratios for skeletal-related events (A), pathologic fractures (B), bone radiation (C), bone surgery (D), and spinal cord compression (E) in Bayesian network meta-analysis versus placebo in cancer patients with bone metastases. Abbreviation: CrI, credibility interval.

Table 3. Network meta-analysis results

Intervention	Placebo	Pamidronate	Ibandronate	Zoledronate	Denosumab
Placebo					
SREs		0.55 (0.41–0.72)	0.74 (0.40–1.38)	0.57 (0.41–0.77)	0.49 (0.31–0.75)
Pathologic fractures		0.84 (0.63–1.18)	0.67 (0.36–1.29)	0.61 (0.43–0.86)	0.50 (0.32–0.79)
Radiation		0.67 (0.52–0.86)	0.81 (0.48–1.30)	0.70 (0.52–0.96)	0.51 (0.35–0.75)
Pamidronate					
SREs	0.52 (0.35–0.78)		1.35 (0.74–2.54)	1.04 (0.75–1.44)	0.91 (0.58–1.42)
Pathologic fractures	0.92 (0.64–1.32)		0.79 (0.39–1.57)	0.72 (0.46–1.09)	0.59 (0.35–0.97)
Radiation	0.52 (0.35–0.78)		1.21 (0.69–2.13)	1.04 (0.70–1.54)	0.77 (0.48–1.18)
Ibandronate					
SREs	—	—		0.77 (0.46–1.28)	0.67 (0.37–1.19)
Pathologic fractures	—	—		0.91 (0.54–1.55)	0.74 (0.41–1.38)
Radiation	—	—		0.87 (0.58–1.31)	0.63 (0.39–1.01)
Zoledronate					
SREs	0.61 (0.48–0.77)	0.94 (0.72–1.23)	0.77 (0.62–0.95)		0.87 (0.64–1.17)
Pathologic fractures	0.58 (0.43–0.78)	1.02 (0.45–2.31)	0.91 (0.67–1.23)		0.82 (0.62–1.09)
Radiation	0.61 (0.48–0.77)	0.94 (0.72–1.23)	0.87 (0.69–1.10)		0.73 (0.57–0.92)
Denosumab					
SREs	—	—	—	0.87 (0.72–1.05)	
Pathologic fractures	—	—	—	0.82 (0.69–0.98)	
Radiation	—	—	—	0.73 (0.63–0.85)	

Data are shown as odds ratios (posterior mean with 95% credibility intervals) for each pairwise comparison of interventions, based on direct evidence alone (lower left) or direct and indirect evidence (upper right). Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions. Abbreviations: —, no data; SRE, skeletal-related event.

evaluated efficacy in reduction of skeletal morbidity period rate (SMPR) [48–50] and three denosumab phase II clinical trials [51–53]. We also excluded a study that treated patients after 12–15 months of zoledronate [54] because the focus of that study was patients with naïve BTAs treatment. Excluding studies with a different definition of what constitutes an SRE resulted in a smaller but more robust NMA. The quality of any NMA is only as good as the weakest link in the network. All studies included in this NMA were of moderate to good quality (Table 2), improving the validity of the NMA results. The

included studies were similar with regard to average age of patients, sex, number of lesions at baseline, and other patient characteristics. Importantly, patient characteristics were not significantly correlated with treatment success. This reduced the potential for heterogeneity across trials and limited resulting bias in the NMA.

Stopeck et al. [14] and Henry et al. [13, 43] did not mention the number of SREs by type in their studies, whereas Fizazi et al. [12] listed the number of SREs by type. Consequently, SREs by type were analyzed only in prostate cancer in the meta-analysis

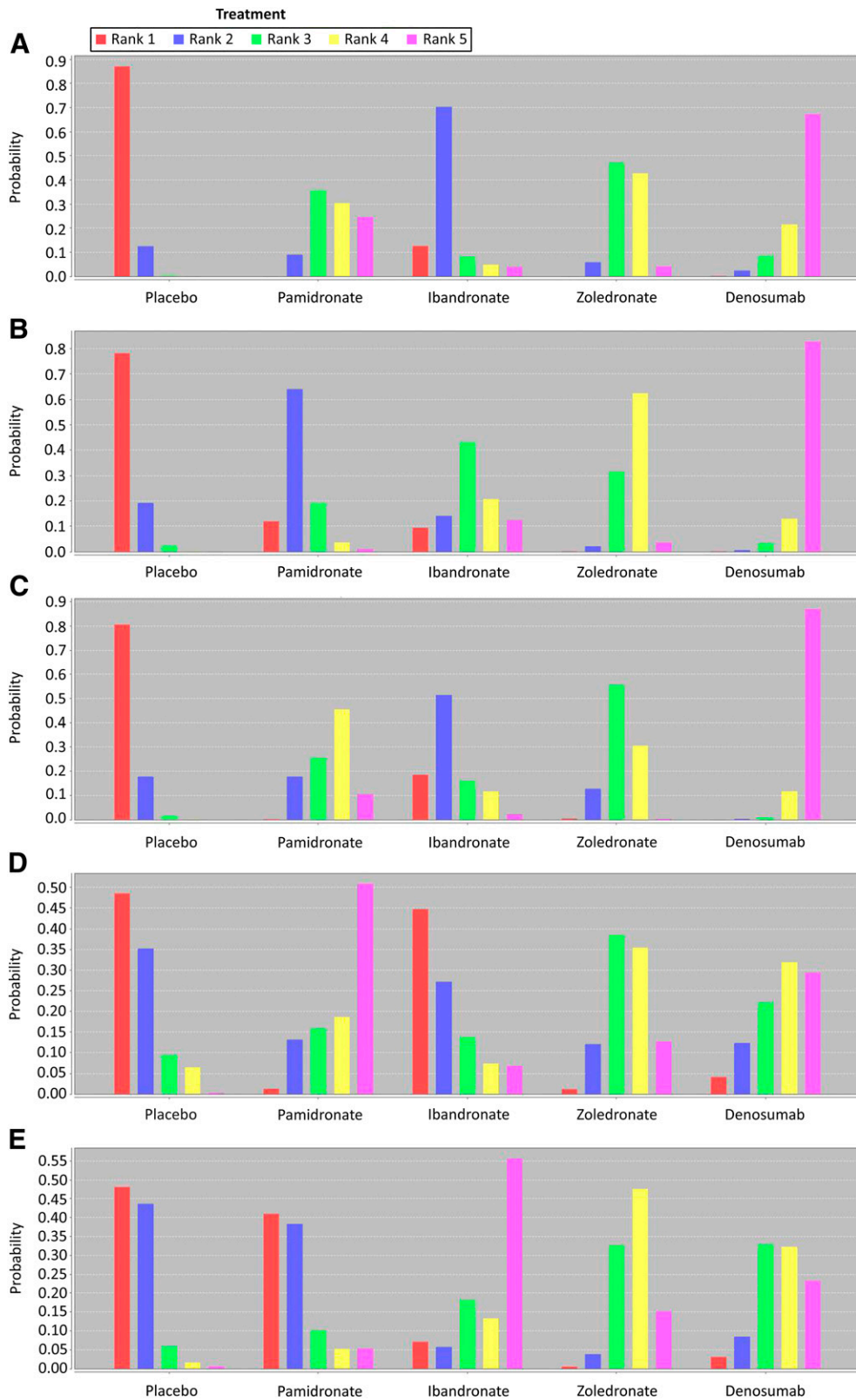


Figure 3. The network meta-analysis rank probabilities for skeletal-related events (SREs) (A), pathologic fractures (B), bone radiation (C), bone surgery (D), and spinal cord compression (E) in cancer patients with bone metastases. The bar chart visualizes the (posterior) probability for each treatment to be best, second-best, and so forth, given the analysis model and the data. Rank of 1 is the worst, indicating the highest incidence of the condition, and rank of 5 is the best, indicating the lowest incidence of the condition.

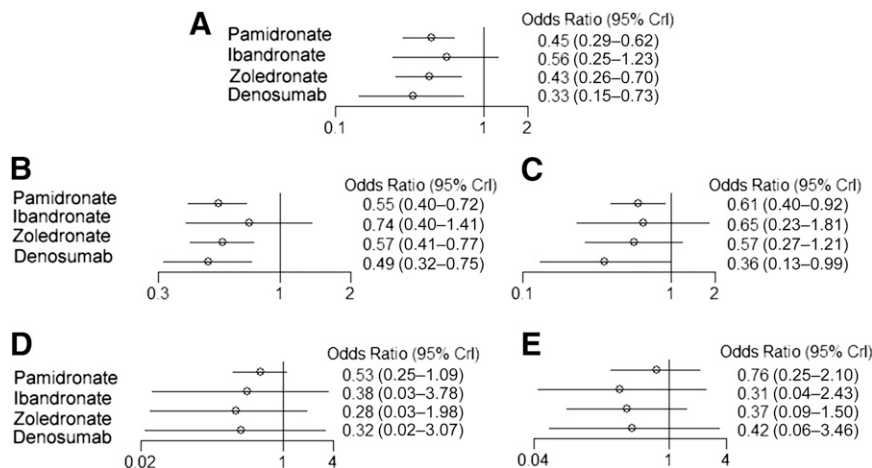


Figure 4. Odds ratios for skeletal-related events (A), pathologic fractures (B), bone radiation (C), bone surgery (D), and spinal cord compression (E) in Bayesian network meta-analysis versus placebo in breast cancer patients with bone metastases.

Abbreviation: CrI, credibility interval.

by Ford et al. [55]. Lipton et al. [56] reported a combined analysis of these three phase III trials, and SREs by type were analyzed. We consulted Amgen and got the data about SREs by type in patients treated in the denosumab (Xgeva) group.

Limitations of the Study

Although RCTs provide the best available evidence for the relative treatment effect of a particular pairwise comparison, the identified RCTs were only placebo-controlled trials. To obtain insight into the relative efficacy of one BTA over another, we had to rely on indirect comparisons. NMA is a method by which multiple meta-analyses of different placebo-controlled (or pairwise) comparisons across a variety of different interventions are performed simultaneously. Consequently, indirect relative efficacy estimates were obtained. Although NMA allows indirect estimates to be calculated, they can be subject to potential biases and uncertainties. NMAs are not randomized comparisons but rather observational findings across studies and thus should be interpreted with caution.

A random-effects model was used for the NMA, which takes into account study heterogeneity and any differences in trial procedures and settings between the included studies that may have influenced results. Berenson et al. [30] treated patients with 0.4, 2.0, or 4.0 mg of zoledronate or 90 mg pamidronate, Rosen et al. [31–33] treated breast cancer patients with either 4 or 8 mg (reduced to 4 mg) of zoledronate or 90 mg pamidronate, Saad et al. [36–40] and Rosen et al. [5, 42] treated patients with either 4 or 8 mg (reduced to 4 mg) of zoledronate or placebo. In order to avoid study heterogeneity, we selected only patients treated with 4 mg of zoledronate, reducing the number of patients enrolled in the meta-analysis. Although >10,000 patients were included in the NMA, as is characteristic of many NMAs, the study was limited by the relatively small number of trials. Some published studies did not report full results, and thus some treatment effects were lost; for example, we obtained the results of only SREs and pathologic fractures from the studies by Rosen et al. [31–33].

Only one ibandronate trial was included because the outcome data reported in the literature were not compatible with those in the present meta-analysis. Despite many studies

evaluating the efficacy of ibandronate in preventing SREs in patients with multiple myeloma [57] and prostate [58], colorectal [59], and breast cancer [48–50], those studies rarely reported outcome measures similar to the ones evaluated in this NMA. Clinical data from such studies were frequently reported as SMPR, defined as the number of 12-week periods with new SREs divided by the number of periods in the study. Tripathy et al. [60] pooled SMPR data from three studies and found a significant reduction in skeletal complications in patients receiving ibandronate compared with those receiving placebo ($p = .004$). They also reported that the risk of a new bone event was reduced by 40% with intravenous and 38% with oral forms of ibandronate in comparison with placebo.

Meaning of the Results

It is of key importance in both pairwise meta-analysis and NMA to not “break” randomization. It is incorrect to simply compare the absolute SRE risk observed with a BTA in one trial with the absolute risk observed with a comparator in another study (i.e., comparing without adjusting for differences in placebo risk). One reason is that part of the observed absolute effect can be attributed to the efficacy of the drug, whereas another part is the result of a placebo effect. One can compare only relative treatment effects, in this case, the relative effects of each BTA relative to placebo.

When looking at each BTA separately, there was a statistically significant difference in favor of denosumab, zoledronate, and pamidronate compared with placebo for the prevention of SREs in cancer patients with BM, whereas ibandronate did not show a difference compared with placebo. NMA showed that the evidence of the efficacy of these drugs in reducing the risks of SREs relates mainly to the reduction in the incidence of pathologic fractures and the need for radiation. A possible explanation for the lower SRE risk reduction observed with oral ibandronate could be poor gastrointestinal absorption of bisphosphonate. An alternative explanation is that only one ibandronate trial was included in the NMA. According to rank probability, denosumab was the best alternative compared with the other BTAs for preventing SREs and reducing the incidence of pathologic fractures and the need for

radiation. Denosumab had the highest rank probability but also had a credibility interval larger than pamidronate; the reason for this may be that there were only three denosumab clinical trials and seven with pamidronate. In addition, in the trials, pamidronate was used mainly for breast cancer patients, with less heterogeneity among patient populations. There is currently a phase III clinical trial of denosumab in an Asian population. When we receive more data from this clinical trial, our results may be different. Based on direct evidence alone, pairwise comparison of BTAs showed that denosumab was superior to zoledronate in reducing the risk of pathologic fractures and radiation, in agreement with the results of Lipton et al. [56].

For the subgroup of breast cancer patients, denosumab and pamidronate also showed efficacy in reducing the risks of SREs and pathologic fractures; however, zoledronate could not reduce the risk of the need for radiation. The fact that we obtained the results of SREs and pathologic fractures from the studies by Rosen et al. [31–33] could be the factor responsible for the reduced effectiveness in terms of lowering the risk of need for radiation. We have contacted Novartis (Basel, Switzerland, <http://www.novartis.com/index.shtml>) to obtain the relevant data but have not yet received it. We hope to use these data, when received, for future studies.

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CONCLUSION

Denosumab, zoledronate, and pamidronate were generally effective (compared with placebo) in preventing SREs in cancer patients with BM. Denosumab was shown to be the most effective of the bone-targeted agents. Reduction in the incidence of pathologic fractures and the need for radiation was the main cause of reduced risk of SREs. The findings of this study highlight the importance of the use of BTAs for cancer patients with BM.

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DISCLOSURES

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