Cancer Management and Research

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ORIGINAL RESEARCH

Efficacy and safety of de-escalation bone-modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis

This article was published in the following Dove Press journal:
Cancer Management and Research

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Background: Compared with application of bone-modifying agents (BMAs) every 4 weeks, it is unclear whether 12-weekly de-escalated therapy can be used as a substitute strategy.

Methods: A systematic search of PubMed, EMBASE, and the Cochrane Register of Controlled Trials until November 22, 2017, was performed. Randomized controlled trials (RCTs) were included to assess skeletal-related event (SRE) rates, adverse events, and bone turnover biomarkers, comparing 12-weekly de-escalated treatments with standard 4-weekly dosage regimens. Risk ratios (RRs) with 95% CIs were pooled in fixed-effect meta-analyses.

Results: A total of eight citations were eligible comprising 2,878 patients: zoledronate (three studies, 2,650 patients), pamidronate (two studies, 68 patients), and denosumab (three studies, 160 patients). Summary RR (0.98; 95% CI 0.87–1.12; P=0.82) for SRE rates between de-escalated and standard arms was produced when seven low risk of bias trials (695 patients) were pooled, and results without statistical significance also appeared in the analysis of adverse events and bone turnover biomarkers. Due to the limited sample size and methodological differences, the data for skeletal morbidity rates (SMRs), time to first SRE, serum C-telopeptide (sCTx) levels, and hypocalcemia were not combined, but systematic review still obtained similar indistinguishableness.

Conclusion: In this meta-analysis of randomized clinical trials, the results "appeared" to show non-inferiority of the 12-weekly treatment. Due to the difference in available data, the results for bisphosphonates are more solid than for the receptor activator of nuclear factor-κB ligand (RANKL) antibodies.

Keywords: bone-modifying agents, bone metastasis, cancer, de-escalated treatment, meta-analysis.

Introduction

Approximately 70% of the patients with multiple myeloma or advanced malignant tumors (especially with highest prevalence in breast and prostate cancers) are associated with a common clinical problem of bone metastasis.[1] Malignant bone diseases caused by bone metastases can severely damage the stability of normal bones and result in life-limiting skeletal-related events (SREs), including pathological fractures and nerve compression, which may require palliative radiotherapy or bone surgery and can also cause hypercalcemia and a decrease in quality of life[2–5] or even lead to a higher risk of death.[6] Bone-modifying agents (BMAs), including bisphosphonates and receptor activator of nuclear factor-κB ligand (RANKL) inhibitor, can inhibit osteoclast-mediated bone resorption.[7] This treatment has been tested to reduce the incidence of skeletal

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http://dx.doi.org/10.2147/CMAR.S176811

morbidity in patients with bone metastases[8–10] and is widely used clinically. However, the best interval of drug delivery is still controversial.

In general, the dosing interval for BMAs is every 3–4 weeks.[11] This dose regimen was developed from studies on hypercalcemia patients and co-administration with standard anti-cancer agents, rather than on convincing pharmacodynamics and contrastive studies.[12,13] The pharmacokinetic studies found that terminal half-lives of bisphosphonate and denosumab were both longer.[14,15] With the prolongation of the overall survival expectancy of the patients with advanced malignant tumors, the toxic effects may increase gradually with the long accumulation periods of BMAs, primarily manifested in jaw osteonecrosis, renal adverse events, hypocalcemia, and bone pain.[16] Therefore, increasing attention has been paid to whether de-escalation dosing could provide the same efficacy as the standard dosage regimen while improving adherence and safety.[17]

We conducted this research to summarize all available evidence from randomized controlled trial (RCT) studies[18–25] regarding the comparison between 12-weekly de-escalation treatments and standard 4-weekly dosage regimens and to provide a quantitative assessment. If de-escalation shows non-inferiority, its clinical application will undoubtedly reduce the cost of medical treatment and the waste of medical resources.

Methods

The present systematic review was in compliance with PRISMA statement[26] and has been registered in the PROSPERO database (CRD42017083426). A complete PRISMA checklist is provided in Table S1.[27,28]

Research question

The research issues are expressed in the framework of population–intervention–comparator–outcomes-study design (PICOS) as "Comparison of the benefit (skeletal morbidity rate [SMR], SRE, time to first SRE) and harm (osteonecrosis of jaw, renal toxicity, bone pain, hypocalcemia) of BMA administration to cancer patients with bone metastases every 12 weeks or every 4 weeks".

Literature-search strategy

Under the guidance of the comprehensive and systematic search strategy formulated by evidence-based experts, PubMed, EMBASE, and Cochrane Library were independently searched by two investigators (CL and LW) and updated until November 22, 2017. No filters, limits, and publication date or language restrictions were enforced. Complete search strategies are shown in Table S2. To test the sensitivity of the search strategy and find any other relevant publications, reference lists of multiple articles and pertinent reviews were checked manually.

Inclusion and exclusion criteria

The article inclusion criteria applied to the stage 1 review (title and abstract reading) were as follows: 1) cancer patients with bone metastasis; 2) randomized clinical trial; and 3) de-escalated treatment (12-weekly) compared with standard treatment (4-weekly) using the same BMAs. Stage 2 review (full-text reading) inclusion criteria for application were as follows: 1) administration contains 4-weekly dose and 12-weekly dose; 2) included at least one end point of the following: SREs, SMR (which was defined as the number of occurrences of any SRE, allowing for only one event in any 3-week interval, divided by the time at risk in years), time to first on-study SRE, adverse events, serious adverse events (SAEs), renal adverse events, osteonecrosis of the jaw, cardiac events, bone pain, radiation to bone, gastrointestinal events, hypocalcemia, or bone turnover marker (urine N-telopeptide [uNTx] or urine N-telopeptide corrected for creatinine [uNTx/Cr] or serum C-telopeptide [sCTx]).

The exclusion criteria were as follows: 1) conference abstracts or 2) not treated with same BMAs or contained different doses in two arms. If data from the same study cohort resulted in more than one publication, data for different outcomes were required to be included, whereas if the results were the same, the most recent or complete report was used to prevent the duplication of data from patients from one cohort.

Data extraction and study quality assessment

Two authors independently performed data extraction and quality assessment, disagreements were resolved by consensus, and a third senior author was consulted when necessary. For all standard research, data collection was performed using a predefined standardized grid (Table 1), including the following entries: first author, year of publication, country, study design information, sample size, mean age, patient inclusion criteria, outcomes assessed, duration, industry funded, and study status. Specific outcomes were separately collected and are shown in Table 2, including SRE, adverse events, SAEs, renal adverse events, osteonecrosis of the jaw, bone pain, radiation to bone, and bone turnover marker (reduction of uNTx).

Table 1 Characteristics of included studies in the meta-analysis

Studies	Country	Study design information	Sample size	Mean age (years)	Patient inclusion criteria	Outcomes assessed	Duration	Industry funded
Zoledronate								
Amadori et al (2013)[18]	Italy	Phase III, prospective, randomized, open-label, non-inferiority (4 mg 4w vs 4 mg 12w)	4w: 216 12w: 209	4w: 59.8 12w: 60.4	Bone metastases, 12–15 months of prior zoledronate use	SMR, SRE, time to 1st SRE, N-telopeptide of type I collagen concentration, adverse events	1 year	Yes
Himelstein et al (2017)[19]	America	Noninferiority, randomized, open-label (4 mg 4w vs 4 mg 12w)	4w: 911 12w: 911	4w: 65 12w: 65	Bone metastases, ≥18 years old, ECOG ≤ 2, creatinine clearance ≥30 mL/min, 11.6 mg/dL > serum calcium level ≥ 8.0 mg/dL	SMR, SRE, pain, ECOG performance status, C-terminal telopeptide levels	2 years	Yes
Hortobagyi et al (2017)[20]	America	Prospective, randomized, multicenter Phase III trial (4 mg 4w vs 4 mg 12w)	4w:200 12w: 203	4w: 59.2 12w: 58.6	Bone metastases, ≥18 years old, ECOG ≤2, life expectancy ≥1 year, >9 months of prior BP use	SMR, SRE, time to 1st SRE, bone turnover biomarkers, adverse events	1 year	Yes
Pamidronate								
Amir et al (2013)[22]	Canada	Randomized, noninferiority, feasibility (90 mg 4w vs 90 mg 12w)	4w: 19 12w: 19	Total: 55	Bone metastases, baseline sCTx levels <600 ng/L, ≥3 months of prior BP use, no treatment change in the 28 days before randomization	SRE, bone turnover biomarkers, pain scores (BPI/FACT-BP)	1 year	No
Addison et al (2014)[21]	Canada	Pilot, randomized, non-inferiority (90 mg 4w vs 90 mg 12w)	4w: 13 12w: 17	NA	Bone metastases, sCTx <600 ng/L, ≥3 months of prior BP use	SRE, bone turnover biomarkers, pain	2 years	No
Denosumab								
Fizazi et al (2009)[24]	Europe, North America	Randomized, open-label, multicenter (180 mg 4w vs 180 mg 12w)	4w: 36 12w: 38	4w: 62 12w: 66	Histologically confirmed carcinomas (except lung) or multiple myeloma, radiographic evidence of ≥1 bone lesion, ECOG performance status of 0, 1, or 2, uNTX ≥ 50 nmol/L/mM, IV BP treatment for ≥8 weeks before enrollment	SRE, time to 1st SRE, adverse events, bone turnover biomarkers, serum denosumab concentration	25 weeks	Yes
Lipton et al (2007)[23,a]	North America, Australia, Europe	Phase II, partially double-blinded,[b] randomized, multidose, active-controlled, international, multicenter, parallel group study (180 mg 4w vs 180 mg 12w)	4w: 43 12w: 43	4w: 57.6 12w: 58.2	Bone metastases, ≥18 years old, no prior IV BP use, ambulatory, adequate organ function, no fracture	SRE, bone turnover biomarkers, adverse events	13 weeks	Yes
Lipton et al (2008)[25,a]	North America, Australia, Europe	Phase II, partially double-blinded,[b] randomized, active-controlled, international, multicenter, multidose, parallel group study (180 mg 4w vs 180 mg 12w)	4w: 43 12w: 43	4w: 58 12w: 58	Bone metastases, ≥18 years old, no prior IV BP use, ambulatory, adequate organ function, no fracture, ECOG ≤2	SRE, bone turnover biomarkers, adverse events	25 weeks	Yes

Notes: [a]For the same outcomes, only the data published in 2008 were included for it had a longer follow-up; otherwise, different outcomes were all needed to be included. [b]Patients receiving denosumab were blinded of assigned dose and frequency, whereas bisphosphonates group was open-label. 4w, 4-weekly dosage regimen; 12w, 12-weekly dosage regimen.

Abbreviations: BP, bisphosphonate; ECOG, Eastern Cooperative Oncology Group; NA, not available; sCTx, serum C-telopeptide; SMR, skeletal morbidity rate; SRE, skeletal-related events; uNTx, urinary N-telopeptide; BPI, Brief Pain Inventory; FACT-BP, Functional Assessment of Cancer Therapy-Bone Pain.

Table 2 Meta-analysis results for end points

Study	BTAs	Outcomes (12-weekly/4-weekly dosage regimen)								
		Total	SRE	AEs	Serious AEs	Bone pain	Renal AEs	Osteonecrosis of the jaw	Radiation to bone	uNTx
Amadori et al (2013)[18]	Zoledronate	209/216	31/33	159/184	21/29	11/13	1/2	4/3	NA	NA
Himelstein et al (2017)[19]	Zoledronate	911/911	253/260	NA	NA	NA	4/10	9/18	NA	NA
Hortobagyi et al (2017)[20]	Zoledronate	203/200	47/44	189/189	51/50	NA	16/19	0/2	23/29	NA
Amir et al (2013)[22]	Pamidronate	19/19	2/2	NA	1/2	NA	0/0	0/0	2/2	NA
Addison et al (2014)[21]	Pamidronate	17/13	4/3	NA	NA	NA	NA	NA	NA	NA
Fizazi et al (2009)[24]	Denosumab	36/38	4/2	NA	NA	NA	NA	NA	NA	23/26
Lipton et al (2007)[23]	Denosumab	43/43	4/6	NA	NA	NA	NA	0/0	NA	NA
Lipton et al (2008)[25]	Denosumab	43/43	NA	41/40	15/16	4/6	NA	NA	NA	32/34
RR from meta-analysis with 95% CI			0.98 (0.87–1.12)	0.96 (0.89–1.04)	0.91 (0.70–1.17)	0.81 (0.42–1.55)	0.67 (0.39–1.16)	0.58 (0.30–1.12)	0.80 (0.49–1.30)	0.90 (0.75–1.08)
I^2 measure of heterogeneity			0%	66%	0%	0%	0%	0%	0%	0%

Abbreviations: AEs, adverse events; BTAs, bone-targeting agents; NA, not available; RR, risk ratio; SRE, skeletal-related events; uNTx, urinary N-telopeptide.

Cochrane Collaboration's assessment tool[29] was used to assess the risk of bias, and special attention was paid to the following items that usually represent the quality of the RCT:[30] random sequence generation, allocation concealment, blinded (participants, personnel and outcome assessment), incomplete outcome data, free of selective reporting, and free of other bias.

Data analyses

Meta-analysis was performed where enough data were available. Binary outcomes were synthesized using risk ratio (RR). All summary estimates were reported with point estimates and corresponding 95% CIs. If data were considered unsuitable for meta-analysis based on study characteristics, a narrative approach to summary of study-specific results was employed. The statistical heterogeneity across studies was assessed using the Cochran Q and I^2 statistics with significance defined as Q test ≤0.10 or I^2 >50%.[31] The random-effects model was selected as a result of the existence of significant heterogeneity; if not, the fixed-effect model was performed to combine results. Due to the limitations of available data, sensitivity or subgroup analyses were not executed. The analyses described earlier were implemented through Review Manager 5.3 (Cochrane Collaboration, Oxford, UK).

Results

Search results

The flow diagram illustrates the identification process of electronic search and study selection based on eligible and excluded trials (Figure 1). Our systematic literature search identified 8,989 potentially relevant publications; after duplicate removal and the first screening of titles and abstracts, 8,974 were excluded. We had a full review for the remaining 15 records, of which seven articles were excluded: one[32] focused upon zoledronate dose rather than dose frequency, one[33] did not include necessary outcomes, one[34] focused on the comparison with denosumab and bisphosphonate, while not providing separate data from each subgroup, and four[35-38] were published as meeting abstracts without end point data. Eventually, eight publications were identified for the meta-analysis.

Study and patients' characteristics

The characteristics and data extraction of qualified studies included in the meta-analysis are summarized in Tables 1 and 2. The age of participants across studies ranged from 55 to 65 years. A total of 2,878 participants from eight RCTs were included. Among the studies, three[18–20] studies evaluated reduced-frequency dosing treatment with zoledronate, two[21,22] with pamidronate, and three[23–25] with denosumab.

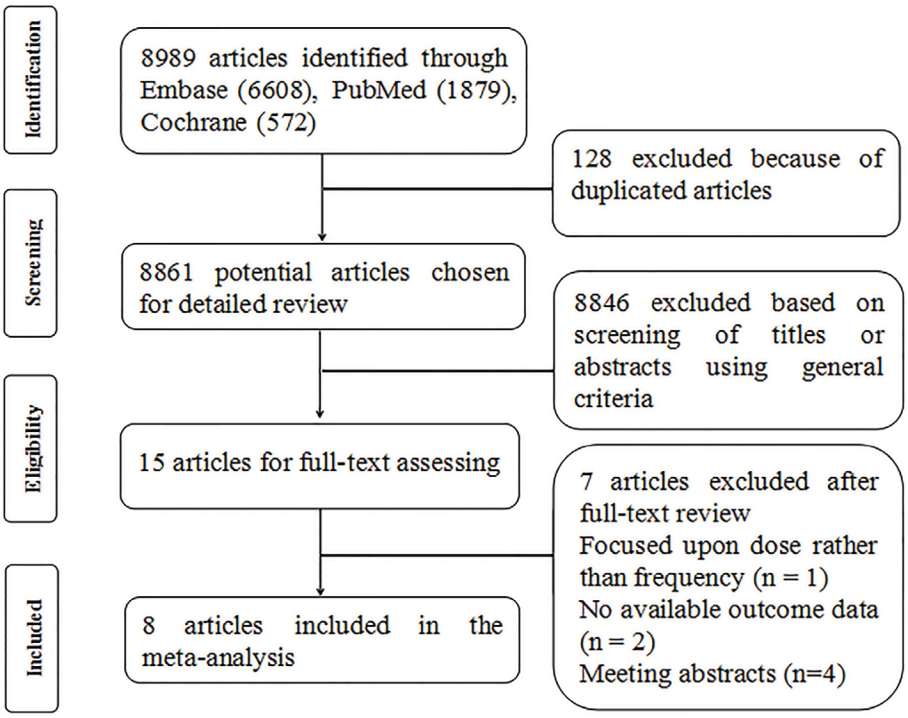

Figure 1 Flow chart of article screening and selection process.

Two of the studies[19,24] involved a series of malignancies with bone metastasis including breast cancer, prostate cancer, and multiple myeloma, and the rest were breast cancer as the main research object.[18,20–23,25] Two articles,[23,25] respectively, reported the results of a study by Lipton et al at different time points (13 and 25 weeks), so the data extracted from the two were considered attributable to the same study. In addition, of all the articles included, two studies were published in 2017,[19,20] two in 2013,[18,22] one in 2014,[21] and three between 2007 and 2009.[23–25] In terms of experimental design, the dose and frequency were consistent across studies using zoledronate (4 mg), pamidronate (90 mg), and denosumab (180 mg) every 4 weeks vs every 12 weeks.

Quality assessment

All included articles[18–25] were evaluated for risk bias using the Cochrane Collaboration tools. Four studies[18–20,24] were considered high risk of bias in blinding of the outcome assessment field. Although other articles also showed an uncertain risk of bias in several fields, overall, the majority of RCTs exhibited lower risk of bias (Figure 2).

Findings – SREs

The included studies reported multiple outcome estimates related to the risk of SREs comparing de-escalated with standard dose, including the SRE rate (the proportion of patients with at least one SRE on study),[18–25] the time to first on-study SRE,[19,20] and the SMR.[18,20]

As shown in Figure 3, data for the SRE rates were available in all the included studies. The combined RRs showed that de-escalated was not superior to the standard arm in SRE rates (RR 0.98; 95% CI 0.87–1.12; P=0.82) with no significant heterogeneity (I^2=0%; P=0.96).

Among the ZOOM study,[18] the SMR ratio (4-weekly arm vs 12-weekly arm) was 0.97 (95% CI 0.60–1.57; P=0.896). In addition, the mean (SD) SMR was 0.50 (1.50) and 0.46 (1.06) events annually for de-escalated vs the standard arm in the OPTIMIZE-2 study.[20] Both findings suggested that the 12-weekly de-escalated was not inferior to the 4-weekly treatment. Regarding the time to first SRE, there was no statistically significant difference between treatment arms (HR 1.06; 95% CI 0.70–1.60; P=0.79) for OPTIMIZE-2.[20] Median times to first SRE were also reported by Himelstein et al,[19] which were 15.7 vs 16.8 (4-weekly arm vs 12-weekly arm). As a result of the differences in data type, no consolidation analysis for SMR or time to first SRE was conducted.

Bone radiotherapy, as one of the important definitions of SRE, was also, respectively, analyzed in two studies (12-weekly arm: 25 events; 4–weekly arm: 31 events).[20,22] Differences with no statistical significance between the two arms are shown in the pooled analysis (RR 0.80; 95% CI 0.49–1.30; P=0.36) (Figure 4).

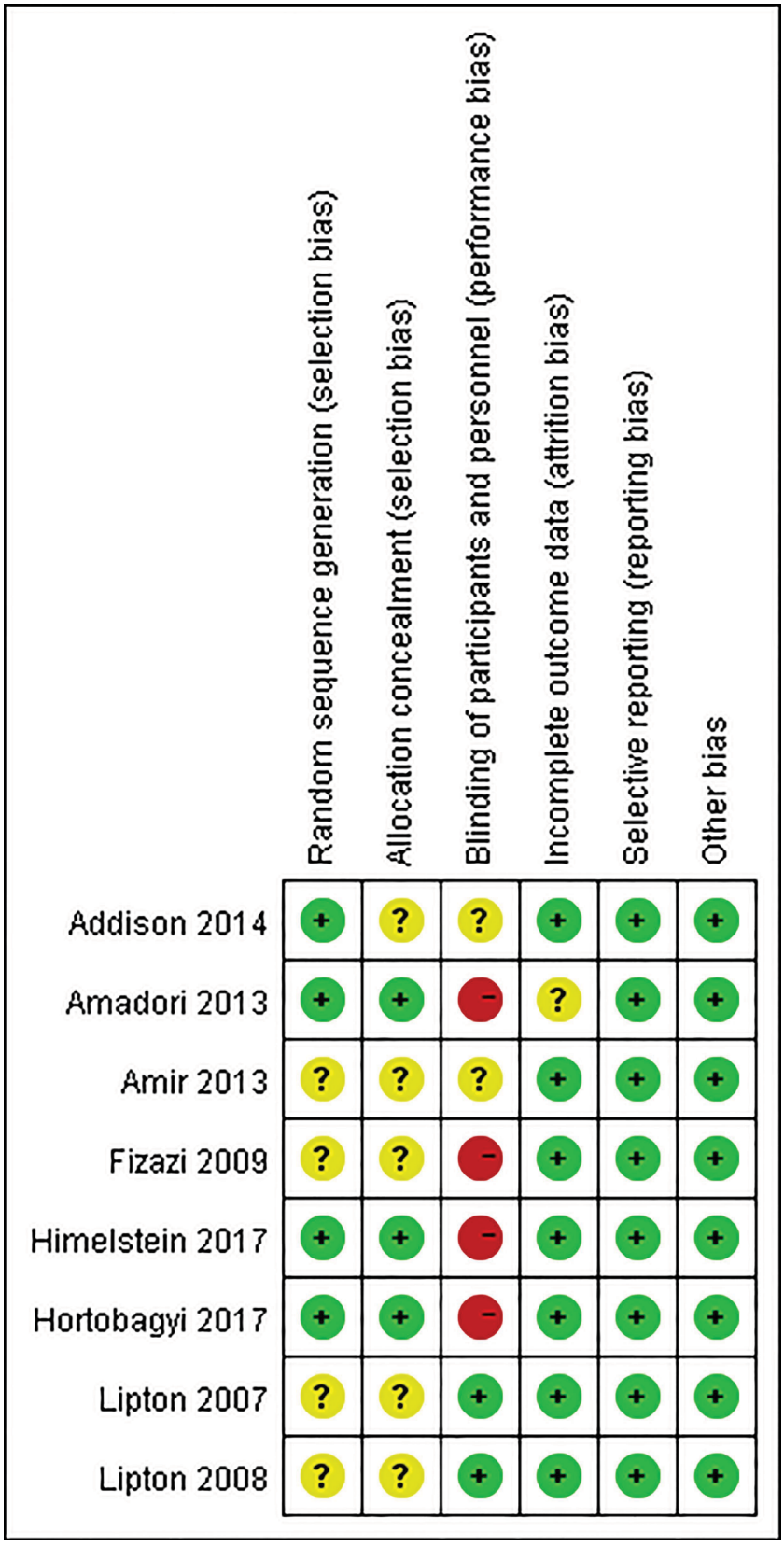

Figure 2 Risk of bias assessment.
Note: Green represents low risk of bias; red represents high risk of bias; and yellow represents unclear risk of bias.

Finding – adverse events

A series of data of side effects and toxicities were analyzed. Overall, AEs occurred in 802 patients (12-weekly arm: 389 events; 4-weekly arm : 413 events) and SAEs occurred in 185 patients (12-weekly arm: 88 events; 4-weekly arm: 97 events). Summary RRs were produced, respectively, RR 0.96 (95% CI 0.89–1.04; *P*=0.38) for AEs and RR 0.91 (95% CI 0.70–1.17; *P*=0.44) for SAEs, both were not statistically significant, and high statistical heterogeneity (I^2=66%; *P*=0.05) was observed for AEs (Table 2 and Figure 5), whereas there was no significant heterogeneity (I^2=0%; *P*=0.78) in SAEs (Table 2 and Figure 6).

In addition, we conducted a meta-analysis of several common toxic outcomes. The results all showed no statistically significant reductions. Only two studies[18,25] have reported bone pain data, the comparison showed a summary RR of 0.81 (95% CI 0.42–1.55; *P*=0.52) between de-escalated (15 events) and standard (19 events) arms, and low statistical heterogeneity was found (I^2=0%; *P*=0.71) (Figure 7). Data for renal adverse events were available from four studies.[18–20,22] Similar indifference was found (RR 0.67; 95% CI 0.39–1.16; *P*=0.15) between de-escalated (21 events) and standard (31 events) arms with low statistical heterogeneity (I^2=0%; *P*=0.55) (Figure 8). Five studies[18–20,22,23] provided available data for osteonecrosis of the jaw, but only three[18–20] were included in the meta-analysis for the presence of 0 events in both groups.[22,23] Comparison showed a summary RR of 0.58 (95% CI 0.30–1.12; *P*=0.11) between de-escalated (1,385 events) and standard (1,389 events) arms, and low statistical heterogeneity was observed (I^2=0%; *P*=0.38)

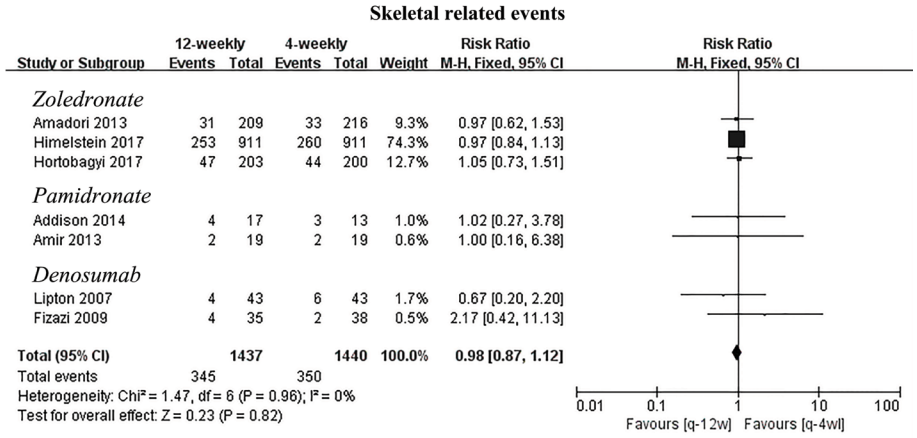

Figure 3 Meta-analysis results for skeletal-related events.

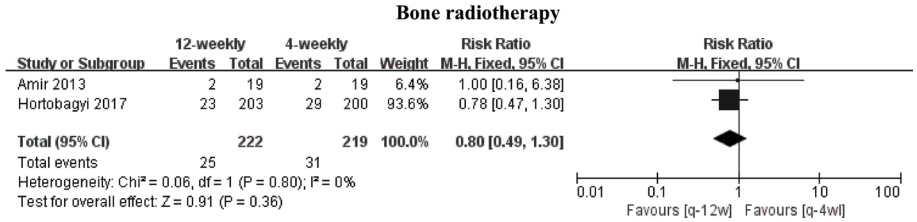

Figure 4 Meta-analysis results for bone radiotherapy.

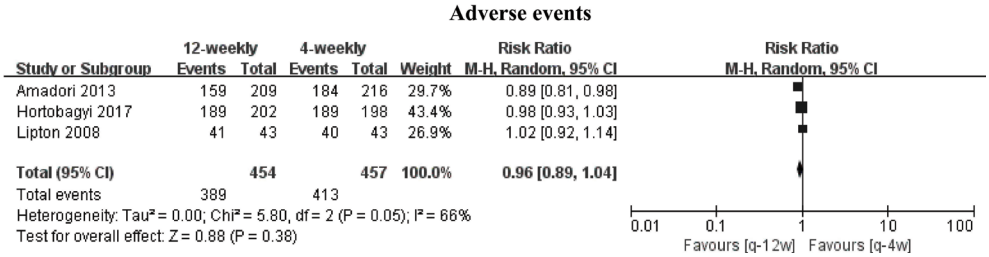

Figure 5 Meta-analysis results for adverse events.

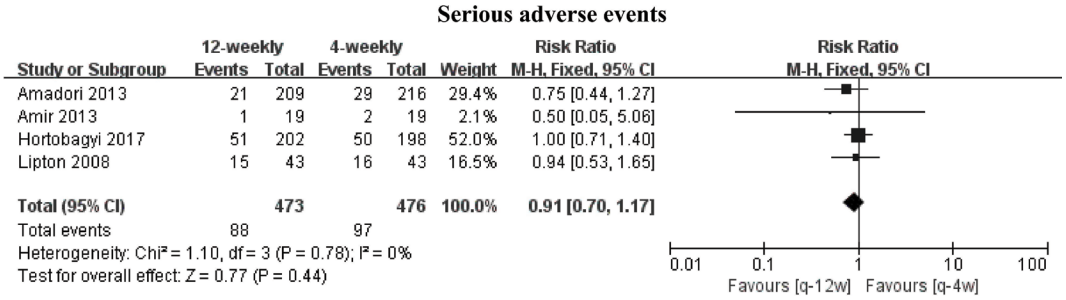

Figure 6 Meta-analysis results for serious adverse events.

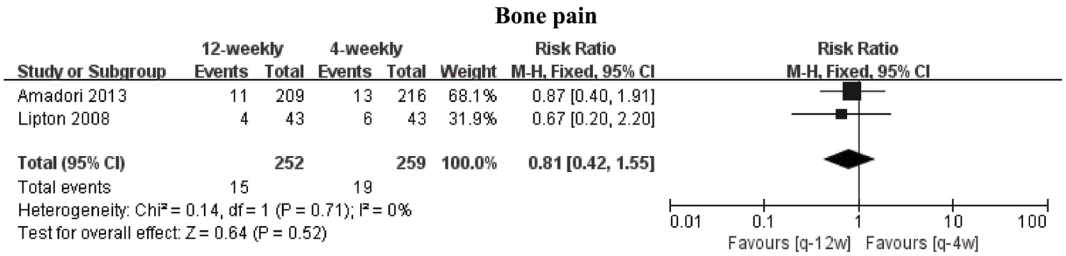

Figure 7 Meta-analysis results for bone pain.

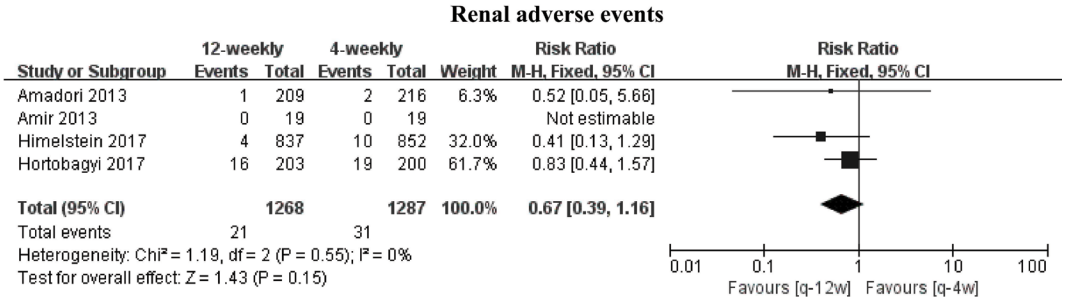

Figure 8 Meta-analysis results for renal adverse events.

(Figure 9). Finally, we did not carry out meta-analysis for hypocalcemia because there was only one set of available data. The research[19] showed that regardless of any grade of hypocalcemia or grade 4 hypocalcemia, no significant differences existed between the 4-weekly group and the 12-weekly group.

Finding – bone turnover biomarkers

The study of Amadori et al[18] provided a significant increase in the N-terminal telopeptide concentration in the 12-weekly group vs 4-weekly group from 6 months (12.2% vs –2.3%; *P*=0.0111) to 12 months (12.2% vs 0.0%; *P*=0.0465). However, this open-label result was not reproduced by a double-blind design of Hortobagyi et al.[20] When we gathered the other available data,[24,25] no statistically significant results (RR 0.90; 95% CI 0.75–1.08; *P*=0.37) were obtained (Figure 10).

The research on sCTx also showed different results. Addison's research[21] based on the REFORM cohort provided a statistically significant greater increase in sCTx (median of 131 vs 17, *P*=0.034) when comparing treatment group 2 (12-weekly arm) with group 1 (4-weekly arm). However, the observation point was only at baseline and week 12, when sCTx levels were measured for 48 weeks, the outcome changed (73.7% in control arm; 68.4% in de-escalated arm; *P*=0.64). No statistical analysis was performed for sCTx due to heterogeneity of the data.

Discussion

Dosing intervals have increasingly been questioned, although the standard application of BMAs is once every 4 weeks, which was obtained from studies of hypercalcemia patients who received anticancer agents[39] and has long been guiding

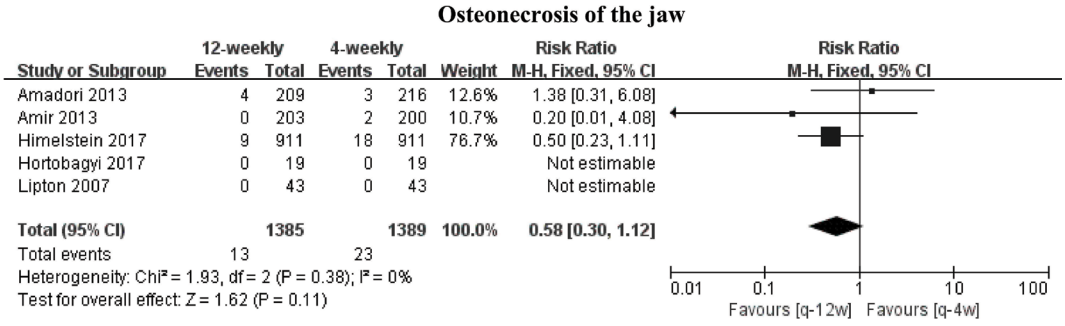

Figure 9 Meta-analysis results for osteonecrosis of the jaw.

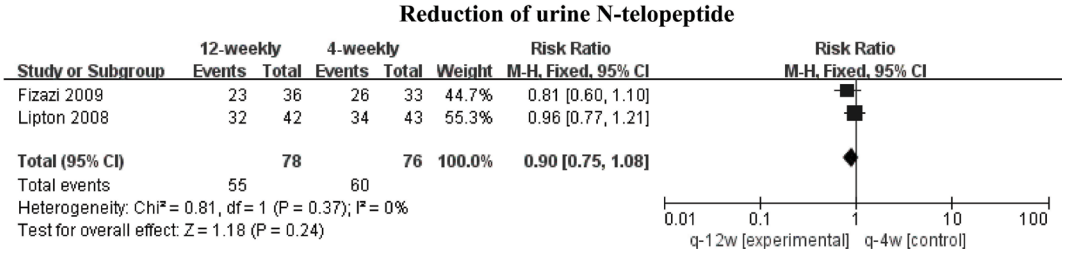

Figure 10 Meta-analysis results for reduction of urine N-telopeptide.

clinical practice.[10,40] Terminal treatment of cancer patients, especially palliative care, requires a shift from "problem-based, disease-oriented" care to "goal-oriented, integrated" care. The balance between the long-term use of BMA-related side effects[41] and the therapeutic benefits of advanced cancer patients needs deliberation. Thus, increasing interest is focused on the de-escalated treatment strategies. If curative effects of de-escalation treatment to less frequent dosing is concordant with administration of 4-weekly, it can effectively reduce health care costs and relieve medical pressure.[42]

The primary outcome is health-related quality of life in this research. The results showed that the 12-weekly de-escalated treatment regimen is not inferior to the 4-weekly dosage regimen for patients with bone-metastatic cancer, regardless of whether they had completed the standard 1 year of BMA treatment before, which challenged the current guidelines.[43–45] The incidence of SRE is a composite frequently used end point of skeletal complications in patients with bone metastases.[46,47] We had observed that the average probability of SREs in different experiments was of great disparity. This finding is not only due to the different frequency requirements for imaging but also because of different decision-making models and treatment thresholds among different clinicians. Although the nature of the SRE is uncertain but still plausible, no statistical significance was shown in the final results between study arms. For frequencies of adverse events and toxicity, although limited to different measuring tools, part of the study of small sample data and not sufficient follow-up time, overall, the results showed non-inferiority of the de-escalated treatment. The role of bone turnover biomarkers as a substitute for subsequent SRE risks is increasingly questioned,[48] and it is still a common clinical method used because it is simpler and easier.[4,49] The results were observed to be different in these studies, but we observed that with the extension of follow-up time and the increase in sample size, the bone turnover biomarker levels tended to not be different between the two groups. In fact, we do not have much hope for a positive outcome for the de-escalated arms; the end is really the same. However, de-escalated scheduling is sufficient to satisfy our predefined definition of non-inferiority. Meanwhile, the limitations of data should be taken into consideration, and its clinical feasibility remains to be verified by large sample experiments. At that time, indiscrimination between the two groups may have a substantial impact on medical decisions.

Since 2000, the American Society of Clinical Oncology (ASCO) guidelines have suggested the use of BMAs indefinitely.[16] For this long-term treatment model, a larger interval of medication will undoubtedly reduce the cost for patients. Actually, the current guidelines recommend a "one size fits all" approach.[50] It is suggested that all patients receive the same dose and frequency of BMAs, regardless of their potential risks or needs, which is obviously unreasonable in the current era of personalized medicine. For example,

with different pharmacokinetic and efficacy properties, denosumab, as a new bisphosphonate alternative drug,[51] was invariably observed to be marginally more effective than zoledronate in preventing SREs and improving quality of life.[52,53] Meanwhile, excellent effectiveness brings a considerable extra cost. The study of Shapiro et al[54] has shown that the mean cost of the treatment strategy is nine-fold higher for denosumab than generic zoledronate every 3 months. Therefore, making appropriate treatment strategies is a test to clinicians. What is important is to limit medical waste and economic loss caused by the overuse of the treated individuals while guaranteeing their health and rights.

There are several limitations to this study that should be mentioned, as well. First, the study contained different BMA types and the duration of BMAs used before enrollment and did not always report common clinical end points. Therefore, certain studies tend to play a dominant role in inherently few research samples when carrying out a specific end point summary analysis. Second, the duration of BMAs in these studies is noteworthy, because the life expectancy of partial cancer patients with bone metastases may be close to or shorter than the median length of follow-up of these studies, especially for the special group of elderly patients.[55] Additionally, with the aggravation of the disease, the loss of follow-up becomes common. Both may lead to inability to fully evaluate the relationship between exposure and outcome. In addition, our research only included the patients with breast cancer, prostate cancer, and multiple myeloma, although bone metastases are common in many types of cancers.[56] Several studies (NCT02051218; NCT00320710; NCT00320710; and NCT02721433) have not included other types of cancer patients as well. Therefore, whether the results can be generalized to other types of cancers is still uncertain and needs further investigation. What has to be further mentioned is that the sample size is very limited, especially for RANKL inhibitor. This may result in the instability, even false positive rate, of the outcomes to a certain extent. Despite these limitations, it is worth noting that there is consistency in all trial results. There were no signs of significant differences between the de-escalation and control arms for different BMAs used and outcome events.

Conclusion

After summarizing and analyzing all available data obtained to date, there appears to be no difference in outcomes between 12-weekly de-escalated therapy and 4-weekly dosage regimen. The longer-interval dose is a better choice, both from a health care resource perspective and a financial perspective. It is important to determine whether each type of cancer can benefit from this and whether the high heterogeneity of SRE risk among different individuals is suitable for unified Clinical Governance. Further precision research is needed in the future to adequately advise clinicians and patients on the optimal dosage regimen of BMAs in various clinical settings.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (grant number: 81473513).

Author contributions

The research project was designed by Cun Liu, Lu Wang, and Changgang Sun; organized by Cun Liu, Lu Wang, Lijuan Liu, Jing Zhuang, Shifeng Tang, Fubin Feng, Jinmei Zhang, and Tingting Zhang; and executed by Cun Liu and Lu Wang. Statistical analysis was designed by Cun Liu, Lu Wang, Tiansong Zhang, Chundi Gao, and Huayao Li; executed by Cun Liu, Lu Wang, Tiansong Zhang, Fubin Feng, Tingting Zhang, and Jia Li; and reviewed and critiqued by Changgang Sun, Lijuan Liu, Chao Zhou, Ruijuan Liu, and Jinmei Zhang. The first draft of the manuscript was written by Cun Liu and Lu Wang, and the manuscript was reviewed and critiqued by Lijuan Liu, Tiansong Zhang, and Changgang Sun. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 PRISMA checklist

	#	Checklist item	Reported on page #
TITLE			
Title	1	***Efficacy and safety of de-escalation bone-modifying agents for cancer patients with bone metastases: A systematic review and meta-analysis***	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1–2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in mean values).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4–5
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	3–5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5–6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5, 7–9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5, 7–9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5–6
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	8–10
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	10

Table S2 Search strategy

Source: PubMed (searched on: November 12, 2017)		
Search	**Query**	**Items found**
#24	Search #13 AND #23	1879
#23	Search #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	8092
#22	Search 615258-40-7	1049
#21	Search 118072-93-8	2851
#20	Search 40391-99-9	2021
#19	Search ((Denosumab) OR Prolia) OR Xgeca	2057
#18	Search "Denosumab"[Mesh]	1049
#17	Search ((((zoledronic acid) OR zoledronic) OR Aclasta) OR Reclast) OR Zometa	4054
#16	Search "zoledronic acid" [Supplementary Concept]	2851
#15	Search (((((pamidronate) OR pamidronate monosodium) OR pamidronate disodium) OR pamidronate calcium) OR Aredia) OR pamidronic acid	2955
#14	Search "pamidronate" [Supplementary Concept]	2021
#13	Search #3 AND #12	12722
#12	Search #11 OR (#7 AND #10)	97885
#11	Search #10 AND bone*	88412
#10	Search #8 OR #9	1120130
#9	Search ((((((micro-metastasis) OR micro-metastases) OR micrometastasis) OR micrometastases) OR metastasis) OR metastatic) OR metastases	1120130
#8	Search "Neoplasm Metastasis" [Mesh]	180784
#7	Search #4 OR #6	155181
#6	Search #5 AND bone*[Title/Abstract]	53967
#5	Search (neoplasm*[Title/Abstract]) OR cancer*[Title/Abstract]	1650801
#4	Search "Bone Neoplasms" [Mesh]	116271
#3	Search #1 OR #2	3662871
#2	Search ((((cancer*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR tumor*[Title/Abstract]) OR sarcoma*[Title/Abstract]	2605327
#1	Search "Neoplasms" [Mesh]	2982032
Source: EMBASE (searched on: November 12, 2017)		
Search	**Query**	**Items found**
#27	#16 AND #26	6608
#26	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	23992
#25	615258-40-7':rn	4909
#24	denosumab OR prolia OR xgeva	6334
#23	denosumab'/exp	6066
#22	118072-93-8':rn	11532
#21	40391-99-9':rn	8996
#20	zoledronic acid' OR zoledronic OR aclasta OR reclast OR zometa	13964
#19	zoledronic acid'/exp	13703
#18	pamidronate OR 'pamidronate monosodium' OR 'pamidronate disodium' OR 'pamidronate calcium' OR aredia OR 'pamidronic acid'	9971
#17	pamidronic acid'/exp	9707
#16	#3 AND #15	109182
#15	#14 OR (#8 AND #12)	110645
#14	#12 AND #13	100952
#13	bone*	1353818
#12	#9 OR #10 OR #11	752553
#11	micro metastasis' OR 'micro metastases' OR micrometastasis OR micrometastases OR metastasis OR metastatic OR metastases	748083
#10	micrometastasis'/exp	5180
#9	metastasis'/exp	559405
#8	#4 OR #5 OR #7	197863
#7	('neoplasm*':ab,ti OR 'cancer*':ab,ti) AND 'bone*':ab,ti	84974
#6	neoplasm*':ab,ti OR 'cancer*':ab,ti	2187167
#5	bone cancer'/exp	87429
#4	bone tumor'/exp	138699

(*Continued*)

Table S2 (*Continued*)

Source: EMBASE (searched on: November 12, 2017)		
Search	**Query**	**Items found**
#3	#1 OR #2	4996953
#2	cancer*':ab,ti OR 'carcinoma*':ab,ti OR 'neoplasm*':ab,ti OR 'tumor*':ab,ti OR 'sarcoma*':ab,ti	3474632
#1	neoplasm'/exp	4404603
Source: Cochrane Library (searched on: November 12, 2017)		
Search	**Query**	**Items found**
#18	#13 and #17	572
#17	#14 or #15 or #16	1787
#16	"denosumab" or "Prolia" or "Xgeva" (Word variations have been searched)	538
#15	"zoledronic acid" or "zoledronic" or "Aclasta" or "Reclast" or "Zometa" (Word variations have been searched)	995
#14	"pamidronate" or "pamidronate monosodium" or "pamidronate disodium" or "pamidronate calcium" or "aredia" or "pamidronic acid" (Word variations have been searched)	551
#13	#12 and #3	3636
#12	#11 or (#7 and #10)	3865
#11	#10 and bone*	3825
#10	#8 or #9	26446
#9	"micro-metastasis" or "micro-metastases" or "micrometastasis" or "micrometastases" or "metastasis" or "metastatic" or "metastases" (Word variations have been searched)	26338
#8	MeSH descriptor: [Neoplasm Metastasis] explode all trees	4537
#7	#4 or #6	7714
#6	#5 and bone*:ti,ab,kw	7583
#5	neoplasm*:ti,ab,kw or cancer*:ti,ab,kw (Word variations have been searched)	119619
#4	MeSH descriptor: [Bone Neoplasms] explode all trees	1239
#3	#1 or #2	144756
#2	cancer*:ti,ab,kw or carcinoma*:ti,ab,kw or neoplasm*:ti,ab,kw or tumor*:ti,ab,kw or sarcoma*:ti,ab,kw (Word variations have been searched)	138258
#1	MeSH descriptor: [Neoplasms] explode all trees	63175