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Bisphosphonates in the Treatment of Patients with Lung Cancer and Metastatic Bone Disease: A Systematic Review and Meta-analysis

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Abstract

Purpose—Bisphosphonates are known to prevent skeletal-related events (SREs) in advanced breast cancer, prostate cancer and multiple myeloma. This systematic review assessed the efficacy of bisphosphonates in preventing SREs, controlling pain, and overall survival in patients with bone metastases from lung cancer.

Methods—We searched MEDLINE, EMBASE, Web of Science, and the Cochrane Library databases through November 10, 2011, for controlled trials that included lung cancer patients with bone metastases treated with bisphosphonates. Two reviewers independently extracted data on pain control, survival, SREs and evaluated the quality of each study. Meta-analyses were performed when there were two or more trials with similar outcomes.

Results—Twelve trials, met our inclusion criteria, and included 1,767 patients. Studies were placebo-controlled or compared bisphosphonates with other modalities (chemotherapy, radiation therapy, or radioisotope therapy), or used different bisphosphonates as active controls. Randomized controlled trials did not report adequate descriptions of randomization procedures, allocation concealment, and blinding, resulting in low quality scores. Patients treated with zoledronic acid + chemotherapy had fewer SREs than those receiving chemotherapy alone (relative risk (RR) 0.81, 95% confidence interval (CI) 0.67-0.97). Pain control improved when a bisphosphonate was added to another treatment modality (chemotherapy or radiation; RR 1.18,

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95%CI 1.0-1.4). Bisphosphonate therapy improved survival compared to controls, but the difference failed to reach statistical significance (mean of 72 days, 95%CI −8.9-152.9).

Conclusions—Treatment with bisphosphonates reduced SREs, improved pain control and showed a trend to increased survival. Bisphosphonates should be used in the treatment of patients with lung cancer and bone metastases.

Keywords

Bisphosphonates; Lung cancer/neoplasm; Bone metastases; Randomized controlled trials; Meta-analysis

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Despite years of research, tobacco prevention programs, and various new treatment modalities, lung cancer remains the leading cause of cancer-related deaths, with a median overall survival time of only 5.8 months after diagnosis and 1- and 2-year survival rates of 22% and 7%, respectively [1]. Thirty percent of patients with lung cancer can develop osteoblastic metastases and up to 40 percent of patients can develop osteolytic or mixed bone metastases [2]; 55% of these will experience one or more skeletal-related events (SRE) over a median follow-up period of 6 months [3];. Those, who already have experienced an SRE, are at higher risk of developing subsequent events [3, 4]. SREs include pathologic fractures, spinal cord compression, bone radiation or bone surgery, and hypercalcemia of malignancy [3-8], and they are associated with significant reductions in physical, functional, and emotional well-being, quality of life and performance status [3, 9]. Furthermore, pathological fractures or other SREs can render patients ineligible for anti-neoplastic treatments, resulting in further tumor progression and a decrease in overall survival [10, 11].

Since the 1990s, bisphosphonates have become a mainstay of the management of bone metastases from various cancers [12-14]. Bisphosphonates are synthetic analogues of pyrophosphate that bind to hydroxyapatite and are then internalized by osteoclasts, inducing apoptosis of the osteoclasts [15]. There are three Cochrane systematic reviews examining the efficacy of bisphosphonates in metastatic bone disease in breast and prostate cancer, and in multiple myeloma [8, 16, 17], but little is known about the effects of bisphosphonates on bone metastases from other solid tumors such as lung cancer, bladder cancer, gastrointestinal malignancies, renal cell carcinoma, melanoma and metastatic cancer with unknown primary [3, 9]. There is also a gross under usage of the bisphosphonates reported in non-small cell lung cancer (NSCLC) patients with metastatic bone disease [18]. The primary objective of this study was to systematically review the efficacy of various bisphosphonates in reducing SREs and bone pain, improving survival in patients with bone metastases from lung cancer. Additionally, we also summarized the evidence on other secondary outcomes (e.g., biomarkers, disease progression, and quality of life) and head-to-head comparisons of the different bisphosphonates used in lung cancer.

METHODS

Study Design

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement to guide us in our review and reporting of findings [19].

Data Sources and Search Strategy

Comprehensive electronic searches in MEDLINE, EMBASE, Web of Science, and Cochrane Library databases were performed until November 10, 2011, with no language restrictions. The detailed search strategy is presented in Appendix 1. Relevant published abstracts and articles were selected. Additionally, hand searching was done to identify

relevant studies in the retrieved articles. In addition, a review of the clinicaltrials.gov website was performed to identify other ongoing or completed trials eligible for review. Authors of abstracts were contacted to obtain additional data but none responded to our request.

Study Selection

Studies were screened and independently selected by 3 reviewers (NS, MLO and GP) in pairs and disagreements were solved by consensus. Eligible studies were controlled clinical trials including lung cancer patients with bone metastases as confirmed by the authors treated with a bisphosphonate in at least one of the intervention groups, either alone or combined with other treatments such as chemotherapy, radiation therapy, or radioisotope therapy, and a comparison (control) group. Because in the real world, patients will receive multi-modality treatments concomitantly, supportive treatments and co-interventions prior to or after the bisphosphonate treatments were allowed. Any type of bisphosphonate was considered eligible, without restrictions on dose, route, frequency, or duration of treatment. The control group could have received placebo or an active control (a different bisphosphonate, chemotherapy, radiation therapy, radioisotope therapy, or any combination of these modalities). We excluded studies that did not include patients with bone metastases from lung cancer or those with the main objective not involving bisphosphonates. Additionally, we excluded observational studies, basic science studies, mixed population trials with non-retrievable data for lung cancer patients.

Data Extraction

Data were extracted independently by 3 reviewers (NAS, MLO and GP) including: 1) General study information; 2) Characteristics of participants; *3) Characteristics of intervention*; *4) Characteristics of control*; and *5) Outcome variables:* SRE included fracture, radiation or surgery to bone, cord compression and/or hypercalcemia of malignancy. Any methods for pain measurement were allowed (visual analogue scale, numerical rating scale, verbal rating scale, 6-point McGill-Melzack pain questionnaire). We used the category “pain controlled” for categories defining effective control, significant improvement, complete or partial remission; and “pain not controlled” for categories with no improvement, exacerbation or no effect. Overall survival was measured in days since patients were allocated to study group. Secondary outcomes included biomarkers (i.e., serum N-telopeptide (NTX) and serum C-telopeptide (CTX) of collagen type I, urine NTX and bone alkaline phosphatase), time to first SRE, bone lesion progression, overall disease progression, performance status, quality of life, and toxicity reports. Appendix 2 shows the different definitions of SRE and other outcome measures used by each included study. The quality of each trial was evaluated independently by 3 reviewers (NS, MLO and GP) using the Cochrane Back Review Group questionnaire to assess risk of bias (0 referred to lowest quality and 11 to highest quality) [20, 21]. We evaluated each trial using 1=“yes” and 0=“no or don’t know” for selection, performance, attrition, detection, and reporting biases. A trial with a cumulative score of 0 to 6 was considered “low-quality” with a higher risk of bias, and a trial with a cumulative score of 7 to 11 was considered “high-quality” with a lower risk of bias.

Data Analysis and Synthesis

For this review, we have use only published data (full text or abstracts). We used STATA (version 10; College Station, Texas, USA) to perform the analysis [22]. Data was pooled in a meta-analysis when there were more than one trial reporting on the same outcome. A qualitative synthesis was provided for those outcomes reported only by one trial. The I-squared (I^2) statistic was used to assess heterogeneity, an I^2>40% was considered to indicate heterogeneous results. In the absence of heterogeneity, fixed effects models were used to

pool results. When heterogeneity was present, random effects models were used [23]. The Mantel-Haenszel method was used to pool the relative risk (RR) for dichotomous outcomes, and the inverse variance method was used to pool the mean differences (MD) for continuous variables. We set the significance level at α=0.05 for pooled data. Comprehensive Meta-Analysis (version 2; Biostat, Englewood, NJ, USA) was used to compute effect sizes, standard errors, and variances for the survival outcome when data were limited [24].

RESULTS

Eligible Trials and Study Characteristics

Of the 925 records identified from the electronic database searches, 680 abstracts were selected for further review. Twelve studies (17 publications) met the inclusion criteria, including a total of 1,767 participants (Figure 1) [6, 7, 18, 25-39]. Of these, only seven studies reported sufficient data for the meta-analysis. Four studies were published in Chinese and were translated by 3 people (see acknowledgements). Table 1 shows participant and design characteristics of the studies included and Table 1 summarizes the comparison groups used in each study.

Quality Appraisal

Quality scores of the studies ranged from 1 to 4. None of the studies described the method of randomization (e.g., random number table) or allocation concealment (e.g., sealed envelopes). Only three trials described baseline similarity among the groups [25, 27, 36]. Blinding was often not feasible, especially when non-drug treatment modalities (e.g., radiation therapy) were included. One study mentioned adequate double-blinding but did not specify whether the patient or the outcome assessor or care provider were blinded [27]. Because all treatments were multi-modal, none of the trials could avoid co-interventions. Although none of the trials mentioned patient adherence to treatment, 2 trials described patient drop-out owing to side effects or other adverse events such as renal impairment, gastrointestinal problems, or osteonecrosis of the jaw [25, 31]. Overall, seven trials included all randomized or assigned patients in the final analysis, thus providing intention-to-treat analysis [27-32, 37-39]. Two trials were only available in abstract format; therefore no quality assessment was performed [34, 36].

Efficacy outcomes

Table 2 describes efficacy outcomes: SRE incidence, pain control and overall survival, time to first SRE and disease progression, in individual and pooled data from included trials.

SRE incidence—Six studies including 1,170 participants reported SRE. Pooled estimates showed a statistically significant 19% reduction in the risk of developing new SREs within the first 2 years of treatment with zoledronic acid (RR 0.81, 95%CI 0.67-0.97) [6, 7, 27, 31, 35, 36]. Zoledronic acid did not demonstrate a statistically significant difference in the risk of developing SREs compared to ibandronate.

Pain Control—Six studies including 500 participants evaluated pain control (patient-reported pain). All studies used 3 levels to categorize pain control (see Appendix 2). Pooled estimates were not statistically significant. However, from individual studies, when bisphosphonates were added to chemotherapy or radiation therapy, patients in the combined-modality group had significantly better pain control than patients in the group receiving chemotherapy or radiation therapy alone [28-30, 32]. Also, more rapid reduction in pain scores was found in patients receiving zoledronic acid (41.6% vs. 29.3%, p=0.05) compared to ibandronate, which disappeared at three months (66.2% vs. 61.8%, p=0.31) [25]. In a recent small head-to-head comparison, treatment with ibandronate did not lead to

significantly better pain control than clodronate (RR 1.1, 95%CI 0.88-1.4), but the authors mentioned that the monthly intravenous injection schedule of ibandronate was more convenient for patients than the daily intravenous injection of clodronate [26].

Overall Survival—Four studies including 778 participants compared survival following treatment with zoledronic acid plus chemotherapy versus chemotherapy alone [6, 7, 27, 31, 33, 36]. An estimated difference of 72.0 days in median survival was observed favoring the zoledronic acid group compared to controls, but this did not reach statistical significance (p=0.08).

Time to first SRE—Zoledronic acid significantly delayed the time to first SRE compared to placebo (MD 163 days; 95%CI 45.2-**278.8)** [34]. Similarly, patients on zoledronic acid + chemotherapy showed a non-statistically significant longer time to first SRE compared to chemotherapy alone (MD 36 days; 95%CI −312.6-384.6) [36]. Patients in the zoledronic acid group developed their first SRE later than patients in the ibandronate group (median time to develop first SRE=10.2 months for zoledronic acid vs. 9.4 months for ibandronate, p=0.03) [25].

Progression *of bone lesions*—Two studies reported progression of bone lesions, where 'Improvement' was measured as complete remission or partial remission compared to 'no improvement' as no change or progressive disease by imaging modalities [26, 30]. The proportion of patients with no disease progression with or without zolendronic acid was similar (41% vs 39%, p=0.80) [33]. Patients treated with a combination of clodronate and radioisotope therapy had less progression 3 months after treatment began compared to patients who received radioisotope therapy alone (p< 0.05) [30]. After 2 cycles of ibandronate or clodronate, bone disease progression was comparable between the two treatment groups [26].

Overall disease progression—When compared to chemotherapy alone, zoledronic acid + chemotherapy did not result in significantly different time to disease progression (MD 5, 95%CI −41.5-51.9, p=0.8) [31, 33, 36-39]. Tumor response to zoledronic acid and to ibandronate was comparable using Response Evaluation Criteria In Solid Tumors criteria at 3-month follow-up [25].

Performance status and quality of life—Two studies reported improvement in quality of life and functional status (data not shown). Treatment with clodronate combined with radioisotope therapy was more effective than radioisotope therapy alone at improving quality of life at 1 month after treatment was started (75% vs. 47.3%, p<0.05)[30]. Ibandronate and clodronate were similarly effective at improving daily living [26].

Biomarkers—Three trials examined biomarkers including serum NTX and CTX of collagen type I, urine NTX and bone alkaline phosphatase [25, 27, 31]. In a post-hoc analysis zoledronic acid and placebo groups were divided into high (≥64 nmol/mmol creatinine), and normal/low-NTX (<64 nmol/mmol creatinine) subgroups. Within both the zoledronic acid and placebo groups, high NTX levels, compared to normal/low levels, were associated with increased adverse events, although not consistently statistically significant including: SREs (zoledronic acid: RR = 1.3, p=0.3; placebo: RR = 1.5, p=0.2), bone disease progression (zoledronic acid: RR = 1.4. p=0.2; placebo: RR = 2.2, p=0.04), experiencing all-time SREs (zoledronic acid: RR = 1.8, p=0.01; placebo: RR = 1.6, p=0.07), and death (zoledronic acid: RR = 1.3, p=0.1; placebo: RR = 2.4, p=0.001) [27]. When analyzing only patients with high baseline NTX levels, the zoledronic acid group had a significantly reduced risk of death (35%, p=0.02) compared to the placebo group [27]. Patients treated

with zoledronic acid had significantly lower median serum CTX levels at 1 month compared to those in the ibandronate group (reduction in levels = 54.8% vs. 38.2%, p=0.03); however, this difference disappeared at 3 months (reduction in levels = 72.6% vs. 66.4%, p=0.22) [25]. Reductions in median bone alkaline phosphatase levels were not significantly different at 1 and 3 months [25]. Urinary NTX levels were reduced in the zoledronic acid treated group by more than half in the first 3 months compared to placebo [31]. Moreover, those who had lower urinary NTX levels at baseline showed maximum reduction of levels lasting up to 9 months when compared to those with higher levels.

Toxicity—Table 3 shows the frequency of adverse events in the included trials, most commonly transient flu-like and gastrointestinal symptoms. Furthermore, patients assigned to the group with zoledronic acid were 17.8 times more likely to develop flu-like syndrome compared to the group without it. Renal impairment was reported in up to 15% of the patients treated with zoledronic acid [25, 31]. There were also reports of reversible bone marrow suppression with the combination of clodronate, pamidronate and zoledronic acid with other therapeutic modalities [26, 30, 33]. Incidence of osteonecrosis of the jaw was observed in 4 of 87 (5%) patients who receiving zoledronic acid [31].

DISCUSSION

Bisphosphonates are commonly used in patients with breast or prostate cancer with bone metastases or multiple myeloma, and have been shown to be effective in reducing bone pain and the occurrence of SREs, either when used alone or concomitantly with radiation therapy [8, 16, 17, 40-43]. However, bisphosphonates are seldom used in patients with lung cancer and metastatic bone disease. Our systematic review and meta-analysis revealed that bisphosphonates can reduce the risk of developing SREs, and help control bone pain in these patients. We found that patients treated with zoledronic acid, compared to placebo, were 19% less likely to develop SREs. Our findings are consistent with the findings of studies assessing the efficacy of zoledronic acid in treating bone metastases from other types of solid tumors [6, 7, 44, 45]. While subgroup analysis was not possible in our review because data was not available, a prior exploratory analysis showed that duration of bone metastasis (≥2 months vs. <1 month), predominant lesion type (osteolytic vs. osteoblastic), a lymphocyte level >14% were associated with increased risk of developing an SRE in patients with NSCLC [46]. In multivariate models, NTX ≥64 nmol/mmol was associated with a >3-fold increased risk of developing a pathologic fracture [46]. Conceivably, patients with these risk factors could benefit the most from bisphosphonate therapy.

Pain control is a primary objective of the use of bisphosphonates in patients with bone metastases [8, 43, 47]. Pamidronate combined with radiation have been reported to provide better pain relief than radiation alone in patients with breast and lung cancers metastatic to bone [47]. A double-blinded, placebo-controlled randomized trial showed that, compared to placebo, 1,600 mg/day of oral clodronate reduced pain scores and analgesic requirements in patients with bone metastases from tumors that were poorly responsive to chemotherapy [9]. When a bisphosphonate alone was compared to other modalities, treatments such as chemotherapy, radiation therapy, or radioisotope therapy provided better pain control. A meta-analysis of 30 randomized controlled trials in 3,682 subjects evaluating the role of bisphosphonates for the relief of bone pain secondary to metastases from various cancers found that 11 patients would need to be treated for 4 weeks or 7 patients for 12 weeks in order to observe the best pain response in 1 patient [43]. Our meta-analysis in patients with lung cancer revealed that when a bisphosphonate was added to standard treatments as mentioned earlier, the combination treatment resulted in significantly better pain control (18% reduction) than the standard treatments without the bisphosphonate. However, use of bisphosphonate alone was not better than the use of other modalities alone. This suggests

that bisphosphonates are most effective for pain control when combined with other therapies.

Four trials in our review reported survival, with a pooled overall survival benefit of more than 2 months when comparing the patients treated with zoledronic acid plus chemotherapy to chemotherapy alone, albeit the samples were small with a total of 778 participants, and the difference did not reach statistical significance. Due to the shorter life expectancy among patients with metastatic lung cancer compared to the life expectancy of patients with some other metastatic cancers, survival measurement may be challenging. Larger, well-performed randomized trials or well controlled cohort studies may be required to strengthen the evidence on overall survival. Coleman et al., reported the results of 3 randomized controlled trials comparing zoledronic acid vs. placebo in the treatment of more than 1600 patients with metastases to bone from solid tumors (>500 from lung cancer), and showed similar survival in the two treatment groups in the intention-to-treat analysis (RR for zoledronic acid =0.94; p=1.1) [48]. Similarly, in a retrospective cohort study, 50 consecutive patients with stage IV NSCLC with bone metastases who had received zoledronic acid plus chemotherapy were compared with patients who received chemotherapy alone. Patients receiving chemotherapy in combination with zoledronic acid showed a statistically significant increase in survival (238 days vs 133 days, respectively; p=0.03) [18].

We found no differences in the time to disease progression between zoledronic acid + chemotherapy and chemotherapy alone. This was also observed by the Associazione Italiana Pneumologi Ospedalieri chest oncology group. The authors reported similar control over bone disease progression between patients treated with pamidronate and those who received radiation therapy [50].

Overall, bisphosphonates were well tolerated. However, among the studies included in our analysis, Zarogoulidis et al., reported up to a 5% incidence of osteonecrosis of the jaw in patients treated with zoledronic acid [31]. This adverse event has also occurred in studies of zoledronic acid for bone metastases from other cancers. A phase III, multi-center, randomized controlled trial examining zoledronic acid as an adjuvant therapy in patients with stage II or III breast cancer reported 11 (0.7%, 95%CI 0.3;1.1%) cases of osteonecrosis of the jaw in the zoledronic acid group [51].

Zoledronic acid has been extensively studied and has shown superior efficacy compared to other bisphosphonates or placebo in several trials for the treatment of bone metastases from various solid tumors [34, 55-58]. In various reviews by Coleman [59-61], zoledronic acid demonstrated the broadest clinical activity in patients with bone metastases from a wide variety of tumor types. The reported adverse events related to zoledronic acid were generally mild and infrequent, suggesting that the benefits of treatment will typically outweigh the risks [60].

In an economic evaluation from five European countries based on a randomized control trial by Rosen et al., 4 mg (or 8 mg) intravenous zoledronic acid every 3 weeks was shown to be cost-effective when compared to placebo in patients with lung cancer [63, 64]. Outcomes and assumptions about benefits were the reported cost-drivers, while adverse events and administration costs did not influence cost-effectiveness estimates [65]. Zoledronic acid has also received the broadest regulatory approval to be used to treat hypercalcemia of malignancy or bone lesions secondary to multiple myeloma and other solid tumors. In addition to patient preferences for shorter infusion times, the 15-minute intravenous infusion of zoledronic acid was felt to be efficient for infusion centers by increasing patient turnover [66]. Studies are ongoing to examine the use of zoledronic acid as a treatment for cancer with potential antitumoral effects other than the reduction of SREs and bone pain [67-69].

Our meta-analysis had limitations. The quality of the trials was generally poor, often because of barriers to effective blinding which cannot be easily resolved for concomitant therapies such as chemotherapy or radiation which may vary among patients. Furthermore, although a trend in improved survival was observed in patients receiving bisphosphonates, the sample sizes of the studies were small and some results did not reach statistical significance. There were 4 studies reporting combined data on both small cell and NSCLC and separate data could not be extracted. Small cell lung cancer is considered distinct from NSCLCs. It exhibit more aggressive behavior, with rapid growth, early spread to distant sites, and great responsiveness to chemotherapy and radiation. Although, bisphosphonates, in particular zolendronic acid, are associated with improved outcomes; this effect may differ between both types of lung cancer. Larger, well-powered, high quality randomized clinical trials could establish the effect of bisphosphonates on the each disease subtype. There were no controlled trials providing data on the efficacy of newer RANKL inhibitors such as denosumab in patients with lung cancer only, therefore, no trials comparing denosumab to bisphosphonates were included in this review. Further studies should evaluate the efficacy of this agent compared to bisphosphonates in patients with lung cancer.

In summary, bisphosphonates (zolendronic acid, pamidronate, and clodronate) reduced SREs and when added to other treatment modalities (e.g., chemotherapy, radiation therapy, radioisotope therapy) resulted in better pain control, quality of life, and less progression of bone lesions than the other therapies alone. Our findings suggest that bisphosphonate therapy is indicated in the treatment of patients with lung cancer and metastatic bone disease.

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Appendix

Appendix 1:

Search strategy

1	exp DIPHOSPHONATES/
2	(Bisphosphon* or Bifosfonatos* or Biphosphon* or Difosfonatos* or Diphosphon*).mp.
3	(alendronate* or fosamax* or adrovance* or fosavance* or adronat* or arendal* or alendros* or onclast* or “alendronic acid*”).mp.
4	(clodronate* or bonefos* or ostac* or loron* or clodron* or “clodronic acid*”).mp.
5	(etidronate* or didronel* or didrocal* or “etidronic acid*”).mp.
6	(ibandronate* or boniva* or bondronat* or “ibandronic acid*”).mp.
7	(incadronate* or bisphonal* or “incadronic acid*”).mp.

8	(minodronate* or recalbon* or bonoteo* or “minodronic acid*”).mp.
9	(neridronate* or “neridronic acid*”).mp.
10	(olpadronate* or “olpadronic acid*”).mp.
11	(pamidronate* or aredia* or pamifos* or pamisol* or “pamidronic acid*”).mp.
12	(risedronate* or actonel* or optinate* or “risedronic acid*”).mp.
13	(tiludronate* or skelid* or “tiludronic acid*”).mp.
14	(zoledronate* or aclasta* or zometa* or “zoledronic acid*”).mp.
15	or/1-14
16	exp LUNG NEOPLASMS/
17	((lung*1 or pulmonary*) adj10 (cancer* or neoplas* or carcinoma* or tumor* or tumour*)).mp.
18	((NSCLC or SCLC) and (lung*1 or pulmonary* or cancer* or neoplas* or carcinoma* or tumor* or tumour*)).mp.
19	(pancoast adj10 (syndrom* or cancer* or neoplas* or carcinoma* or tumor* or tumour*)).mp.
20	(exp CARCINOMA, SQUAMOUS CELL/ or (squamous and scc).mp.) and (exp LUNG/ or (lung*1 or pulmonary*).mp.)
21	(exp ADENOCARCINOMA/ or adenocarcinoma*.mp. or (malignan* adj3 adenoma*).mp.) and (exp LUNG/ or (lung*1 or pulmonary*).mp.)
22	or/16-21
23	15 and 22
24	exp NEOPLASM METASTASIS/ and exp “BONE AND BONES”/
25	((prevent* or inhibit*) adj10 metasta*).mp. and (exp “BONE AND BONES”/ or exp BONE NEOPLASMS/)
26	(bone*1 adj10 (metasta* or antimetasta* or anti-metasta*)).mp.
27	exp BONE NEOPLASMS/sc
28	or/24-27
29	23 and 28
30	(animals not (humans and animals)).sh.
31	29 not 30
32	randomized controlled trial.pt.
33	controlled clinical trial.pt.
34	random allocation.sh.
35	double blind method.sh.
36	single blind method.sh.
37	(randomized or randomised).ti,ab.
38	or/32-37
39	31 and 38
40	clinical trial.pt.
41	CLINICAL TRIALS AS TOPIC/
42	(clinical* adj10 trial*).ti,ab.
43	((singl* or doubl* or tripl* or trebl*) adj10 (blind* or mask*)).ti,ab.
44	placebo*.ti,ab.

45	randomly.ti,ab.
46	trial.ti,ab.
47	groups.ab.
48	drug therapy.fs.
49	RESEARCH DESIGN/
50	CONTROL GROUPS/
51	or/40-50
52	31 and 51
53	52 not 39

Appendix 2:

Definition of Outcome Measures

Outcomes	Definition	Used by
Primary		
Skeletal Related Events[a]	Radiation therapy or surgery to bone, spinal cord compression event or a pathologic bone fracture event Not specified	Scagliotti[37-39], Francini[25], Rosen (Hirsh [6, 7, 27] Zaragoulidis[31, 35], Hirai[36], Kritikos[34]
Pain[b]		
	Visual analogue scale (0-10) 4 categories: 0 = no pain, 1-3 mild, 4-6 moderate, 7-10= severe BPI	Zaragoulidis[31, 35], Guo[26]
	Verbal rating scale for analgesia effects 6-point McGill-Melzack pain questionnaire (reponses: no pain, mild pain, discomforting/moderate pain, distressing/severe pain, horrible/extremely severe pain, excruciating/life threatening pain)	Rosen (Hirsh)[6, 7, 27] Zheng[32] Francini[25], Li[28]
	Subjectively evaluated by patients and by analgesic needs (permanent pain, night-time pain, pain only occurring during movement) with 4 categories: no pain = no pain and no analgesics, mild pain = patient cannot rest, but needs no analgesics moderate pain = patient cannot rest and needs analgesics, severe pain = patient cannot sleep and needs nacotics.	Su[30], Zhang[29]
Pain control	'Significant improvement' = pain decreased by 2 levels; 'Effective control' = pain decreased by 1 level; 'No effect '= no change	Francini[25], Guo[26], Zhang[29], Zheng[32]
	Complete remission = 100% of pain alleviated; Partial remission = ≥ 50% of pain alleviated; No improvement = pain was not effectively controlled	Su[30]
	No change = no pain improvement; Effective control = pain decreased by ≥1 level; Exacerbation = patients experience worse pain	Li[28]

Outcomes	Definition	Used by
Overall Survival	Days since beginning bisphosphonate therapy	Scagliotti[37-39], Zaragoulidis[31, 35], Rosen (Hirsh)[6, 7, 27]
	From the days of diagnosis to the date of death due to any cause (up to 1 year) Not Specified	Pandya[33] Hirai[36]
Secondary		
Time to the First Skeletal Related Event	The time from randomization to the date of occurrence of the first SRE	Scagliotti[37-39]
	The time from the date of the first dose of study drug to the first documentation of bone metastasis	Pandya[33]
	Not Specified	Hirai[36], Kritikos[34]
Biomarkers	S-CTX and B-ALP NTx nM BCE	Francini[22] Zaragoulidis[28, 32], Rosen (Hirsh)[5, 6, 24]
Bone lesion progression	CT scan (measurement of lesions approximately every 3 months)	Rosen (Hirsh)[6, 7, 27]
Overall disease progression	Response Evaluation Criteria in Solid Tumors (RECIST), CT scans and then new symptom occurrence	Pandya[33], Francini[25]
	Modified Southwest Oncology Group	Rosen (Hirsh)[6, 7, 27]
Time to disease progression	The time from the date of the first dose of intervention to the date of first documented progression death due to underlying cancer, or date to loss of follow-up	Pandya[33], Zaragoulidis[31, 35],
	Not Specified	Hirai[36]
Performance status	ECOG	Rosen (Hirsh)[6, 7, 27]
Quality of life	FACT-G	Rosen (Hirsh)[6, 7, 27]
Serious Adverse Events	Not specified	Zheng[32], Zaragoulidis[31, 35]

[a] Percentage of participants with >1event;

[b] All studies used 3 levels for pain categorization, we therefore, defined “pain not controlled” for categories with no improvement, exacerbation or no effect and we defined “pain controlled” for categories defining effective control, significant improvement, complete or partial remission

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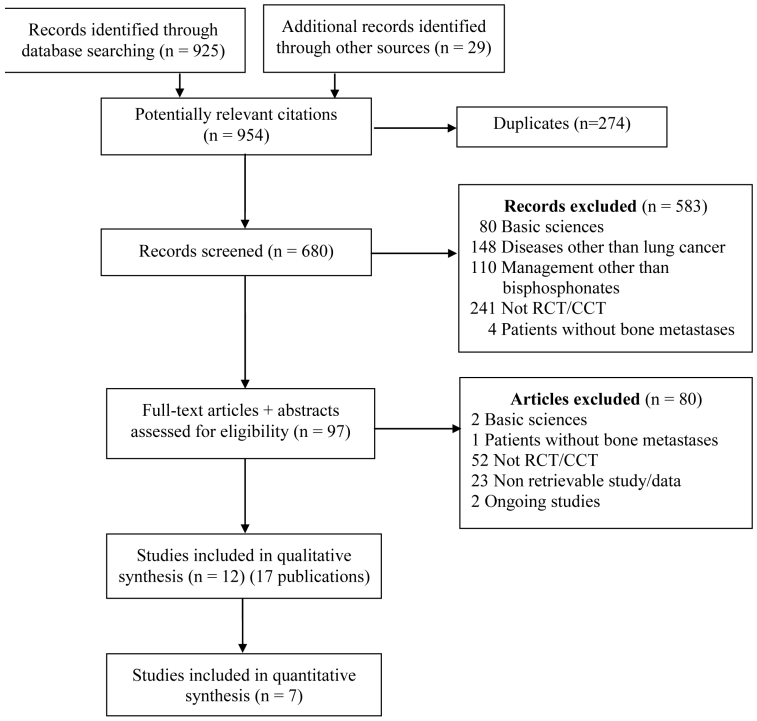

Figure 1.
Study selection flowchart following PRISMA recommendations[19].

Table 1

Study and Patient Characteristics

Study	Country	Center	Follow-up	Groups (n)	Mean age,years	Male, %	NSCLC Stage	Bias Scale[a]
Zhang [29]	China	Single	21 days	Pamidronate (13) Pamidronate + radiation (12) Pamidronate + Chemotherapy (15) Radiation (40)	55.5	58.7	NR[f]	2
Su [30]	China	Single	3 months	Clodronate (28) Radioisotope ($^{89}SrCl_2$) (19) Clodronate + Radioisotope (20)	58.9	65.7	NR[f]	2
Li [28]	China	Single	NR	Radiation (20) Radioisotope (16) Chemotherapy (19) Clodronate (15) Radiation + chemotherapy (22) Radiation + Radioisotope (25) Clodronate + chemotherapy (24)	58.5	69.5	NR	1
Zheng [32]	China	Single	NR	Pamidronate + chemotherapy (18) Pamidronate + radiation (16) Pamidronate + radioisotope (12) Chemotherapy (15) Radiation (10)	48.5	64.8	NR[f]	2
Guo [26]	China	Single	42 days	Ibandronate (44) Clodronate (42)	51.4	53	NR	2
Kritikos[g,i] [34]	Greece	Single	24 months	Zolendronic acid (NR) Placebo (NR)	NR	NR	NR[f]	-
Rosen [7][6][27]	USA, UK, Canada	Multi	9 months	Zoledronicacid (259) Placebo (123)	63[c]	67	NR	4
Zarogoulidis [31, 35]	Greece	Single	12 months	Zoledronic acid + Chemotherapy (87) Chemotherapy (57)	62[c]	NR	IV	2
Francini [25]	US, Canada	Multi	3 months	Zoledronic acid (28) Ibandronate (27)	64	63.2	IIIB or IV	2
Pandya[h] [33]	Italy	Single	12 months	Zolendronic acid + Chemotherpay (100) Chemotherapy (52)	70[c]	75	IV	3
Hirai [36]	Japan	Multi	12 months	Zolentronic acid + Chemotherapy (50) Chemotherapy (50)	NR	NR	NR	-
Scagliotti[b] [37-39]	Europe	Multi	24 months	Zolendronic acid (226) No treatment[b] (211)	59.6	70.3	IIIA or IIIB	3

NR, not reported; NSCLC, non-small cell lung cancer;

[a]Cochrane Back Review group risk of bias (range 0 to 11, higher values indicate lower bias[20];

[b]All patients had completed primary treatment (surgery, chemotherapy or radiotherapy).

[c]Median age, years;

[d] Post hoc analysis of non-small cell lung cancer patient cohort in RCT by Rosen et al 2004[7, 44];

[e] Standard Deviation;

[f] Included both small cell lung cancer and non-small cell lung cancer;

[g] Data published in abstract form only were included;

[h] Did not include patients with bone metastases;

[i] assuming total number of patients equally distributed between groups (26 + 26 =52).

Table 2

Major efficacy outcomes

	Intervention		Control		Effect size (95% CI)	I^2	p-value
	Events/ n	%	Events/ n	%			
SRE INCIDENCE					*RR for reduced SREs*		
Zoledronic acid vs. placebo							
Kritikos[c] [34]	10/26	38	13/26	50	0.77 (0.41-1.4)		
Zoledronic acid + chemotherapy vs. chemotherapy							
Zarogoulidis[31, 35]	4/87	5	3/57	5	0.87 (0.20-3.8)		
Rosen [7] [6] [27]	124/259	48	74/123	60	0.80 (0.66-0.96)		
Hirai [36]	15/50	30	20/50	39	0.75 (0.44-1.3)		
Scagliotti[d] [37-39]	5/226	2	3/211	1	0.74 (0.39-1.4)		
Pooled M-H	*148/622*	*24*	*100/441*	*23*	*0.81(0.67-0.97)*	*0*	*0.02*
Zoledronic acid vs. ibandronate							
Francini [25]	*5/26*	*19*	*7/27*	*30*	0.74 (0.27-2.0)		
PAIN CONTROL					*RR for better pain control*		
Clodronate vs. radioisotope							
Su [30]	23/28	82	16/19	84	0.98 (0.75-1.3)		
Li [28]	8/15	53	9/16	56	0.95 (0.50-1.8)		
Pooled M-H	*31/43*	*72*	*25/35*	*71*	*0.97 (0.74-1.3)*	*0*	*0.80*
Bisphosphonate alone (clodronate or pamidronate) vs. other modalities [a]							
Su [30]	23/28	82	16/19	84	0.98 (0.75-1.3)		
Li [28]	8/15	53	64/102	63	0.85 (0.52-1.4)		
Zhang [29]	11/13	85	33/40	83	1.0 (0.78-1.4)		
Pooled M-H	*42/56*	*75*	*113/161*	*70*	*0.95 (0.78-1.2)*	*0*	*0.62*
Bisphosphonate combined (clodronate or pamidronate) vs. other modalities [b]							
Su [30]	18/20	90	16/19	84	1.1 (0.84-1.4)		
Li [28]	18/24	75	64/102	63	1.2 (0.91-1.6)		
Zhang [29]	24/27	89	33/40	83	1.1 (0.89-1.3)		
Zheng [32]	41/46	89	16/25	64	1.4 (1.0-1.9)		
Pooled M-H	*101/117*	*86*	*129/186*	*69*	*1.2 (1.0-1.4)*	*0*	*0.01*
Bisphosphonate (combined) vs. bisphosphonate (alone)							
Su [30]	18 /20	90	23/28	82	1.1 (0.87-1.4)		
Li [28]	18/24	75	8/15	53	1.4 (0.83-2.4)		
Zhang [29]	24/27	89	11/13	85	1.1 (0.80-1.4)		
Pooled M-H	*60/71*	*85*	*48/56*	*86*	*1.2 (0.96-1.4)*	*0*	*0.14*
Zoledronic acid vs. ibandronate							
Francini [25]	11/18	61	9/16	56	1.1 (0.62-1.9)		
Ibandronate vs. clodronate							
Guo [26]	36/46	78	31/42	74	1.1(0.88-1.4)		

	Intervention		Control		Effect size (95% CI)	I^2	p-value
	Events/ n	%	Events/ n	%			
SURVIVAL					*Mean difference (days)*		
Zoledronic acid + chemotherapy vs. chemotherapy	**n**	**days** [e]	**n**	**days** [e]			
Zarogoulidis [31, 35]	87	578	57	384	194.0 (80.9-307.2)		
Rosen [7][6][27]	259	187	123	157	30.0 (−65.6-125.6)		
Pandya[f] [33]	100	266	52	206	60.0 (−108.2-228.2)		
Hirai [36]	50	312	50	291	21.0 (−61.7-103.7)		
Pooled I-V	*496*		*282*		*72.0 (−8.9-152.9)*	*55*	*0.08*
TIME TO DISEASE PROGRESSION					*Mean difference (days)*		
Zoledronic acid + chemotherapy vs. chemotherapy	**n**	**days** [e]	**n**	**days** [e]			
Zarogoulidis [31, 35]	87	265	144	150	115.0 (47.9-182.1)		
Pandya [33]	100	132	150	131	0.00 (−0.04-0.04)		
Hirai [36]	50	81	100	78	3.0 (−39.4-45.4)		
Scagliottid [37-39]	226	270	437	339	−69.0 (−109.8- −28.2)		
Pooled I-V	*463*		*831*		*5.2 (−41.5-51.9)*	*87*	*0.83*

n= sample size; SRE, Skeletal Related Events; M-H, Mantel-Haenzel; I-V, Inverse Variance;

[a]Other modalities include: chemotherapy, radiation and /or radioisotopes;

[b]Combined: bisphosphonates with chemotherapy, radiation and/or radioisotopes;

[c]Assuming total number of patients equally distributed between groups;

[d]All patients had completed primary treatment (surgery, chemotherapy or radiotherapy);

[e]Median survival time in days; fDid not include patients with bone metastases.

Table 3

Major toxicity outcomes

		Intervention		Control			
Adverse event (study)	**Comparison group**	**Events/n**	**%**	**Events /n**	**%**	**RR[a] (95% CI)**	**AR[a]**
Flu-like illness							
Zheng [32]	Pamidronate (combined)[a] vs. chemoradiation	4/46	9	3/25	13	0.7 (0.18-3.0)	4
Guo[26]	Ibandronate vs. clodronate	3/44	7	5/42	12	0.6 (0.15-2.3)	5.1
Shucai [29]	Pamidronate (single or combined)[a] vs. radiation	1/40	3	2/40	5	0.5 (0.05-5.3)	2.5
Zarogoulidis [31]	Zoledronic acid + chemotherapy vs. chemotherapy	13/87	17	0[b]/57	0	17.8 (1.1-293.6)	17
Francini [25]	Zoledronic acid vs. ibandronate	6/26	23	2/27	7	3.1 (0.69-14.1)	15.6
Scagliotti [37-39]	Zoledronic acid vs. no treatment	12/224	5	3/213	1	3.8 (1.1-2.1)	4
Gastrointestinal illness							
Su [30]	Clodronate vs. radioisotope	6/48	13	2/19	11	1.2 (0.26-5.4)	2
Li [28]	Clodronate (single or combined) vs. other modalities	38/43	88	44/63	70	1.3 (1.0-1.5)	19
Shucai [29]	Pamidronate (single or combined)[a] vs. radiation	5/40	13	9/40	23	0.56 (0.20-1.5)	10
Zarogoulidis [31]	Zoledronic acid + chemotherapy vs. chemotherapy	15/87	17	0[b]/57	0	20.4 (1.3-334.9)	17
Francini [25]	Zoledronic acid vs. ibandronate	0b/26	0	1/27	4	0.35 (0.01-8.1)	3.8
Scagliotti [37-39]	Zoledronic Acid vs. no treatment	100/224	9	65/213	4	1.5 (0.08-0.23)	15.3
Kidney impairment [c]							
Zarogoulidis [31]	Zoledronic acid + chemotherapy vs. chemotherapy	4/87	5	0[b]/57	0	5.9 (0.33-108.1)	5
Francini [25]	Zoledronic acid vs. ibandronate	4/26	15	1/27	4	4.2 (0.50-34.8)	11.6
Scagliotti [37-39]	Zoledronic Acid vs. no treatment	1/224	5	1/213	1	0.95 (0.06-15.1)	0.02
Decrease in blood counts/ bone marrow suppression							
Su [30]	Clodronate vs. radioisotope	4/48	8	4/19	21	0.4 (0.11-1.4)	12.7
Guo [26]	Ibandronate vs. clodronate	1/44	2	1/42	2	0.95 (0.06-14.8)	0.1
Pandya[d] [33]	Zoledronic acid + chemotherapy vs. chemotherapy	29/98	30	14/52	27	1.1 (0.64-1.9)	2.7
Osteonecrosis of jaw							
Zarogoulidis [31]	Zoledronic acid + chemotherapy vs. chemotherapy	4/87	5	0[b]/57	0	5.9 (0.33-108.2)	5
Francini [25]	Zoledronic acid vs. ibandronate	1/26	4	0[b]/27	0	3.1 (0.13-73.1)	3.8
Scagliotti [37-39]	Zoledronic Acid vs. no treatment	1/224	1	1/213	1	0.95 (0.06-15.1)	0.02

AR, Absolute Risk; CI, confidence interval; RR, relative risk;

[a] Single: no additional treatment modalities used, combined: additional modalities (chemotherapy, radiation therapy, or radioisotope therapy) used;

[b] Numbers not reported in study, '0' events were assumed;

[c] Authors reported: increase in creatinine ≤1 mg/dl (Zarogoulidis et al. [62]), decrease renal function (Francini et al. [23]), and renal failure (Scagliotti et al. [53-55]);

[d] Did not include patients with bone metastases.