Original Research Article
Zoledronate for Metastatic Bone Disease and Pain: A Meta-Analysis of Randomized Clinical Trials

Min Zhu, MD,*§ Rui Liang, MD,*§ Ling-Hui Pan, MD,*§ Bing Huang, MD,* Wei Qian, MD,* Jian-Hong Zhong, MD,† Wei-Wei Zheng, MD,‡ and Chang-Long Li, MD*

Departments of *Anesthesiology and
†Hepatobiliary Surgery, Tumor Hospital of Guangxi Medical University, Nanning;
‡Department of General Surgery, First Affiliated Hospital of Xinxiang Medical College, Xinxiang, P.R. China

Reprint requests to: Rui Liang, MD, Anesthesiology Department of the Tumor Hospital of Guangxi Medical University, He Di Rd. #71, Nanning 530021, P.R. China. Tel: (86)-0771-5313774 (office); Fax: (86)-0771-5330700; E-mail: liangrui05@163.com.

§These authors contributed equally to this work.

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Abstract

Background. Randomized controlled trials (RCTs) have reported different results when using zoledronate to treat skeletal-related events (SREs) and bone pain in patients with metastatic bone disease (MBD), and few have looked at the risks and benefits of long-term use of the drug. This meta-analysis aimed to investigate the efficacy and safety of zoledronate to treat MBD in the short and long-term.

Methods. PubMed, EMBASE, and the Cochrane Library were searched to identify RCTs evaluating zoledronate for MBD. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

Results. Twelve RCTs involving 4,450 patients were included in the meta-analysis. Zoledronate decreased the risk of developing SREs compared with placebo (RR 0.75, 95% CI 0.69 to 0.81, \( P < 0.001 \)). Zoledronate consistently reduced the brief pain inventory (BPI) below baseline compared with placebo at 3, 12, and 24 months. In addition, the likelihood of experiencing a bone pain event was significantly lower in the zoledronate group than in the placebo group (RR 0.83, 95% CI 0.76 to 0.89, \( P < 0.001 \)). While the two groups did not differ significantly in the incidence of nausea (RR = 1.07, 95% CI 0.96 to 1.19, \( P = 0.250 \)), emesis (RR 0.94, 95% CI 0.81 to 1.09, \( P = 0.420 \)), or adverse renal events (RR 1.41, 95% CI 0.94 to 2.11, \( P = 0.09 \)), the zoledronate group showed a significantly higher relative risk of pyrexia (RR 1.43, 95% CI 1.20 to 1.70, \( P < 0.001 \)), fatigue (RR 1.26, 95% CI 1.10 to 1.43, \( P < 0.001 \)), and anemia (RR 1.33, 95% CI 1.14 to 1.55, \( P < 0.001 \)).

Conclusion. Compared to placebo, zoledronate significantly reduced the incidence of bone pain and SREs in patients with MBD for periods as long as 24 months. In addition, zoledronate is generally well tolerated over this long period.

Key Words. Zoledronate; Metastatic Bone Disease; Skeletal-Related Events; Bone Pain; Meta-Analysis

Introduction

Tumor growth in bone results in pain, hypercalcemia, anemia, increased susceptibility to infection, skeletal fractures, compression of the spinal cord, spinal instability, and decreased mobility, all of which compromise the patient’s functional status, quality of life, and survival [1]. Patients with metastatic bone disease (MBD) are at high risk of skeletal-related events (SREs), including pathologic fractures and spinal cord compression. SREs may cause rapid deterioration of the patient’s quality of life, resulting in disability, and reduced function. In addition, patients endure the constant threat of skeletal morbidity over a relatively long period, which increases their emotional distress [2]. SREs are common in patients with advanced breast, prostate, lung, and renal cell carcinomas as these tumors show remarkable affinity for bone.
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Treatment of MBD includes orthopedic management, radiotherapy, surgery, and systemic treatments, such as endocrine therapy, chemotherapy, and bisphosphonates. Antineoplastic treatment options are limited for patients at this stage of the disease, especially for those who are elderly and who have complicating medical conditions. Radiotherapy and/or surgical procedures are applied in order to reduce pain, maintain or restore bone function with neurologic decompression, and control local tumor growth. These approaches should take into consideration the prognosis associated with the primary tumor, as well as the patient’s general health and life expectancy [3]. Patients who respond to systemic anti-metastatic therapy have a good chance of being alive at 3 years after diagnosis, and ~20% will be alive at 5 years [4]. Progress has been made over the last decade in gaining a mechanistic understanding of the factors that drive bone cancer pain [5].

Bisphosphonates are stable analogues of the pyrophosphate molecule that inhibit bone resorption. The analogues accumulate in the mineralized matrix of bone, where they are hydrolyzed by osteoclasts. These synthetic drugs vary in clinical activity and potency because of structural differences in the side chains attached to the central carbon atom. In randomized trials of oral and intravenous (i.v.) clodronate administration to men with hormone-refractory prostate cancer (HRPC) and bone metastases, bisphosphonate treatment transiently reduced bone pain and analgesic use, but the differences from placebo were not statistically significant [6–8]. Similarly, a randomized study investigating the clinical benefits of i.v. pamidronate (90 mg) to treat patients with HRPC and bone metastases failed to demonstrate statistically significant reductions in pain, analgesic use, or rate of skeletal complications compared to placebo [9]. In contrast, zoledronic acid has been shown to be effective in treating patients with bone metastases secondary to prostate cancer as well as other solid tumors [10–12]. In phase III trials, zoledronate (4 mg) has shown broad clinical activity in patients with multiple myeloma or breast cancer [11] and in patients with lung cancer or other solid tumors [12]. However, the results of these studies are inconsistent or controversial. In addition, few studies have assessed the long-term safety and efficacy of zoledronic acid, even though the drug is routinely used in patients with MBD for extended periods of up to two years. Therefore, a meta-analysis is needed to clarify the short- and long-term effects of zoledronate for treating patients with MBD.

Methods

Literature Searches

Literature searches were carried out to identify all relevant randomized controlled trials (RCTs) comparing zoledronate with placebo for treating patients with MBD. PubMed, EMBASE, and the Cochrane Library were systematically searched for all articles published up to October 2011. The search terms used were: zoledronic acid and bone metastasis, and these two terms in combination with zoledronate and bone pain. In each article identified, relevant references were also manually searched.

Selection Criteria

Citations identified in the initial searches were subsequently screened for eligibility using the follow inclusion criteria: (1) patients in the study had at least one site of bone metastasis and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2; (2) the study evaluated the effects of at least one type of zoledronate on SREs or bone pain in patients with any type of MBD; and (3) the study was a placebo-controlled RCT.

Data Extraction

We extracted and combined data from all eligible studies that reported the number of patients with any type of SREs and increases in brief pain inventory (BPI) from baseline at all time points examined. The BPI assesses the intensity and impact of cancer pain on daily functioning [13]. Items were rated on a scale from 0 to 10, and pain scores were grouped into categories of none (score = 0), mild (score 1–3), moderate (score 4–6) or severe (score 7–10) [14]. The numbers of patients suffering from any adverse events (e.g., fatigue, pyrexia, anemia) during each clinical trial were also extracted. Data were extracted independently by MZ and WWZ, and discrepancies were resolved through consensus.

Statistical Analysis

The weighted mean difference (WMD) with 95% confidence interval (CI) was calculated for continuous variables, such as changes from BPI composite pain score at baseline, while relative risk (RR) with 95% CI was calculated for binary outcomes, such as incidence of SREs and adverse events. The heterogeneity of trial results was assessed using the chi-square test and the I^2 measure of inconsistency. A P-value less than 0.1 for the chi-square test was defined as significant heterogeneity [15]. Pooled estimates were generated using a fixed-effects model unless there was evidence of significant heterogeneity, in which case a random-effects model was used. Data analysis was performed using RevMan 5.0. In general, P-values less than 0.05 were considered significant.

Quality Assessment

The methodological quality of the studies included in the meta-analysis was scored using the Jadad composite scale [3]. Widely used to assess the quality of RCTs, this scale incorporates the following five questions: 1) Is the study randomized? 2) Is the study double-blind? 3) Is there a description of withdrawals? 4) Is the randomization adequately described? 5) Is the blindness adequately described? This is a five-point scale, with studies having a score of 2 or less defined as low quality, and studies with a score of at least 3 defined as high quality.
Results

Description of Studies

A total of 150 potentially relevant publications up to October 1, 2011 were systematically identified in PubMed, EMBASE, and the Cochrane Library. Of these, 109 (72%) were excluded because they did not satisfy the inclusion criteria, or they failed to provide sufficient information to determine whether the criteria were satisfied. An additional 29 publications were excluded because they did not examine the SRE and BPI or they were not placebo controlled. In the end, 12 RCTs [16–27] containing 4,450 patients met the inclusion criteria and were included in the meta-analysis (Figure 1).

Characteristics of the included studies are described in Table 1. Five studies evaluated prostate cancer with bone metastases. Others studied other types of primary cancers, including lung cancer with various other solid tumors. All studies in the meta-analysis assessed i.v. zoledronate administered at a dose of 4 mg every 3 or 4 weeks. Ten of the included studies reported that all patients received a 500-mg calcium supplement and 400–500 intravenous units (IU) of vitamin D daily. One study reported that patients did not receive any treatment other than zoledronate. The remaining study showed that patients received palliative radiotherapy on the affected bone using either two fractions of 650 cGy over 24 hours or five fractions of 400 cGy over 4 days (2,000 cGy). The choice of radiotherapy depended on the volume to be irradiated and its vicinity to critical structures.

The mean Jadad score of the studies in the meta-analysis was 3.25 (Table 1). All 12 studies mentioned randomization, and five described the randomization method. Nine trials stated that they were double-blind. Eight reported the number of withdrawals.

Efficacy

Reduction of All SREs

Data for SREs were reported in 10 of 12 trials. The zoledronate group showed a significantly lower rate of SREs than the placebo group (RR 0.75, 95% CI 0.69 to 0.81, \( P < 0.001 \); Figure 2). No heterogeneity was observed \( (P = 0.60, I^2 = 0\%) \). Sensitivity analysis showed that the
pooled result was unchanged by removing low-quality studies with a score of 2 or less [16,18,20,23,24,26].

Mean Change from Baseline Composite BPI Score

Six studies reported data about the BPI composite pain score (Figures 3–5). Zoledronate significantly reduced BPI composite pain scores below baseline at 3 months (WMD 0.53, 95% CI 0.72 to –0.35, \( P < 0.001 \)), 12 months (WMD 0.39, 95% CI 0.62 to –0.16, \( P < 0.001 \)), and 24 months (WMD 0.48, 95% CI –0.77 to –0.19, \( P < 0.001 \)). No significant heterogeneity was observed between studies at any of these three time-points (\( P > 0.50 \) or \( I^2 < 50\% \)).

Table 1  Main patient and treatment characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>N</th>
<th>ECOG (≤2)</th>
<th>N with Prior SREs</th>
<th>Baseline BPI Pain Score*</th>
<th>Intravenous Administration</th>
<th>Jadad Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al., 2003 [25] Placebo</td>
<td>247</td>
<td>215</td>
<td>179</td>
<td>Median 3.3</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>254</td>
<td>218</td>
<td>166</td>
<td>Median 3.5</td>
<td>4 or 8 mg, every 9 months</td>
<td></td>
</tr>
<tr>
<td>Zaghloul et al., 2010 [16] Placebo</td>
<td>20</td>
<td>NR</td>
<td>20</td>
<td>2.1 ± 2.04</td>
<td>4 mg, every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>214</td>
<td>197</td>
<td>2.0 ± 1.98</td>
<td>for 24 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saad and Eastham, 2010 [17] Placebo</td>
<td>208</td>
<td>190</td>
<td>NR</td>
<td>2.1 ± 2.04</td>
<td>4 mg, every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Vera Hirsh et al., 2008 Placebo</td>
<td>123</td>
<td>146</td>
<td>126</td>
<td>&lt;3.25, N = 67</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>259</td>
<td>300</td>
<td>247</td>
<td>&lt;3.25, N = 144</td>
<td>weeks for 9 months</td>
<td></td>
</tr>
<tr>
<td>Saad et al., 2007 [19] Placebo</td>
<td>208</td>
<td>190</td>
<td>78</td>
<td>2.1 ± 2</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>214</td>
<td>197</td>
<td>66</td>
<td>2 ± 2</td>
<td>weeks for 9 months</td>
<td></td>
</tr>
<tr>
<td>Smith et al., 2007 [20] Placebo</td>
<td>203 (all ≥1)365</td>
<td>215</td>
<td>≥2, N = 301</td>
<td>4 mg, every 3 weeks</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>440</td>
<td></td>
<td></td>
<td>for 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saad, 2005 [21] Placebo</td>
<td>208</td>
<td>190</td>
<td>78</td>
<td>2.1 ± 2</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>214</td>
<td>197</td>
<td>66</td>
<td>2 ± 2</td>
<td>weeks for 15 months</td>
<td></td>
</tr>
<tr>
<td>Kohno et al., 2005 [22] Placebo</td>
<td>113</td>
<td>101</td>
<td>113</td>
<td>2.7</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>114</td>
<td>101</td>
<td>114</td>
<td>2.6</td>
<td>weeks for 13 months</td>
<td></td>
</tr>
<tr>
<td>Hirsh et al., 2004 [23] Placebo</td>
<td>247</td>
<td>215</td>
<td>180</td>
<td>NR</td>
<td>4 mg, every 4 weeks</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>254</td>
<td>211</td>
<td>167</td>
<td>for 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipton et al., 2003 [24] Placebo</td>
<td>19</td>
<td>18</td>
<td>18</td>
<td>Median 3.3</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>27</td>
<td>24</td>
<td>Median 4.3</td>
<td>weeks for 9 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maung, 2002 Placebo</td>
<td>208</td>
<td>189</td>
<td>NR</td>
<td>NR</td>
<td>4 mg, every 3 weeks</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>[26] zoledronate</td>
<td>214</td>
<td>197</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saad et al., 2002 [27] Placebo</td>
<td>208</td>
<td>190</td>
<td>78</td>
<td>2.1 ± 2</td>
<td>4 or 8 mg, every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>zoledronate</td>
<td>214</td>
<td>202</td>
<td>66</td>
<td>2 ± 2</td>
<td>weeks for 9 months</td>
<td></td>
</tr>
</tbody>
</table>

* Values in this column refer to the mean ± SD, unless otherwise noted.

BPI = bone pain index; ECOG = Eastern Cooperative Oncology Group; NR = not reported; SRE = skeletal-related events.

Figure 3  Comparison of the mean change from baseline composite BPI score at 3 months of zoledronate treatment or placebo.
**Adverse Events**

Table 2 lists the adverse events of particular interest, without adjusting for the median duration of therapy. The incidence of pyrexia was significantly higher in the zoledronate group (27.6%) than in the placebo group (19.4%), corresponding to an RR of 1.43 (95% CI 1.12 to 1.70, *P* < 0.001). Pooled RR estimates for the following adverse events were also significantly higher for patients receiving zoledronate than for those receiving placebo: anemia (30.4% vs 22.9%, RR 1.33, 95% CI 1.14 to 1.55, *P* < 0.001), nausea (40.8% vs 38.3%, RR 1.07, 95% CI 0.96 to 1.19, *P* < 0.001), and fatigue (34.1% vs 27.2%, RR 1.26, 95% CI 1.11 to 1.43, *P* < 0.001). At the same time, a statistically smaller proportion of zoledronate patients reported bone pain (49.1% vs 59.4%, RR 0.83, 95% CI 0.76 to 0.89, *P* < 0.001). No statistically significant differences were noted between zoledronate and placebo in the incidence of emesis (25.0% vs 26.5%, RR 0.94, 95% CI 0.81 to 1.09, *P* = 0.420) or adverse renal events (11.1% vs 8.0%, RR 1.41, 95% CI 0.94 to 2.11, *P* = 0.09), and no significant heterogeneity between trials was detected (*P* > 0.50 or *I*² < 50%). In all trials in the meta-analysis, the proportion of patients with decreased renal function was not significantly different between the 4 mg zoledronate and placebo groups.

**Discussion**

This meta-analysis, which involved a total of 4,450 patients, suggests that zoledronate is more effective than placebo at preventing all SREs and bone pain in cancer patients with MBD for periods of up to 24 months. In addition, zoledronate is generally well tolerated in patients with MBD over the same long period. The pooled population in this meta-analysis represents the largest randomized cohort of patients treated with zoledronate for MBD.

**Table 2**  Meta-analysis of adverse events for zoledronate and placebo in patients with MBD

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. of Studies Included</th>
<th>Patients Reporting Event/Total</th>
<th>RR (95% CI)</th>
<th><em>P</em> Value</th>
<th><em>P</em> Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>6</td>
<td>509/1,037</td>
<td>0.83 (0.76 to 0.89)</td>
<td>&lt;0.001</td>
<td>0.94</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>423/1,037</td>
<td>1.07 (0.96 to 1.19)</td>
<td>0.25</td>
<td>0.14</td>
</tr>
<tr>
<td>Emesis</td>
<td>6</td>
<td>259/1,037</td>
<td>0.94 (0.81 to 1.09)</td>
<td>0.42</td>
<td>0.004</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>354/1,037</td>
<td>1.26 (1.10 to 1.43)</td>
<td>&lt;0.001</td>
<td>0.74</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5</td>
<td>227/823</td>
<td>1.43 (1.20 to 1.70)</td>
<td>&lt;0.001</td>
<td>0.54</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>281/923</td>
<td>1.33 (1.14 to 1.55)</td>
<td>&lt;0.001</td>
<td>0.33</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>5</td>
<td>65/594</td>
<td>1.35 (0.95 to 1.93)</td>
<td>0.09</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Zoledronate has high-binding affinity to hydroxyapatite of bone and potent antiresorptive activity on the overall skeleton, and the site of metastasis to bone is more likely to be its primary site of action. A significant decline in urinary markers of bone after treatment of the patients with zoledronate, but not with placebo, indicates the inhibitory activity of osteolytic bone disease [27]. Different from lung cancer and breast cancer with the bone metastasis, bone metastases of the prostate cancer in the x line usually appears as bone lesions, but the morphological and biochemical studies of the bone tissue show that osteoblastic lesions has a more significant high level of bone synthesis and bone absorption mark molecular than osteolytic lesions [28,29]. Osteolysis is the key step of bone metastase from prostate cancer caused by abnormal bone metabolism. Although metastases radiation test results for bone mineral density increase, bone hardness significantly weakened because of bone growth disorder. Therefore, the inhibition of any one of the three kinds of cells, which is the osteolytic cell, is the key to improve bone metabolism and reduce the risk of fracture [30].

Our literature search identified several systematic reviews evaluating the efficacy of bisphosphonates in the prevention of SREs [31–34]. Three meta-analyses evaluated patients with MBD originating from breast cancer [32], advanced prostate cancer [33], and multiple myeloma [34]. Those analyses found that bisphosphonates led to an approximately 10% absolute risk reduction for SREs compared to placebo, consistent with the present meta-analysis. However, those meta-analyses must be interpreted with caution since they pooled different bisphosphonates together, and we know that members of this synthetic drug family vary in clinical activity and potency. In contrast, the present meta-analysis focused specifically on the bisphosphonate zoledronate, commonly used to prevent SREs in cancer patients with MBD. Our results indicate that it is generally more effective than placebo at preventing SREs a over long period of time. This suggests that the current clinical practice of administering this drug for a long period is justified.

In our meta-analysis, zoledronate also significantly reduced bone pain, as indicated by the change from baseline BPI composite pain scores. The pain reduction was modest but for a long term: BPI composite pain scores were lower than baseline and placebo scores at 3, 12, and 24 months. Previous meta-analyses reported effects out to only 4 or 8 weeks, with a few studies going to 12 weeks. At the same time, since previous meta-analyses did not measure pain in a standardized way, data on whether bisphosphonates relieve pain are so limited that robust conclusions are difficult. Nevertheless, in a study of 3,682 patients with cancer treated with bisphosphonates, pooled data showed that a significantly greater proportion of patients receiving bisphosphonate experienced pain relief than did patients receiving placebo [35].

Safety analysis in the present meta-analysis suggests that zoledronate is well tolerated over 24 months of treatment, with overall rates of adverse events such as nausea and emesis similar to those with placebo [22]. In addition, bone pain, particularly severe bone pain, was reported more frequently in the placebo group. However, a higher proportion of patients treated with zoledronate reported fever and fatigue, which are typically associated with the acute-phase reaction that often accompanies the first infusion of an i.v. bisphosphonate [36]. Thus, these adverse events are a class effect, not specific to zoledronate. Since adverse renal events are known to be associated with i.v. bisphosphonates, they were analyzed in detail in the present meta-analysis. The proportion of patients with decreased renal function was not significantly different between the 4 mg zoledronate and placebo groups after implementation of a 15-minute infusion (100 mL) in June 1999. A subsequent protocol amendment in June 2000 reduced the dose of the 8 mg zoledronate treatment arm to 4 mg because of renal toxicity [27]. Moreover, monitoring guidelines have been developed to minimize the risk of permanent effects, and modified dosing regimens have been established for patients with decreased renal function [37]. Zoledronate has been associated with slightly higher risk of elevated serum creatinine, but the difference from placebo did not achieve statistical significance. Even so, serum creatinine levels should be monitored in patients receiving zoledronate therapy, because renal clearance of zoledronate in patients with bone metastases of malignancy is correlated with their CLCR (creatinine clearance) [38]. No cases of osteonecrosis of the jaw were reported. But recent guidelines recommend performing dental procedures before initiating bisphosphonate therapy to minimize the risk of developing osteonecrosis of the jaw. It is also recommended that if dental procedures needed during therapy, the least invasive procedures should be used; in addition, bisphosphonate therapy may be withheld until the surgery site has healed [39]. Taken together, the adverse events associated with zoledronate were predictable, transient, mild to moderate in intensity, and easily managed with supportive care.

The main limitations of the included studies are in the procedures used to conceal the treatment allocation, which were often inadequate. Another primary limitation of the present meta-analysis is the lack of comparison with other bisphosphonates in clinical use. In particular, ibandronate was not included because the outcome data reported in the literature are not compatible with those in the present systematic review. Though numerous studies evaluate the efficacy of ibandronate in preventing SREs and bone pain relief in patients with multiple myeloma [40], prostate [41], and breast cancer [42], they rarely report outcome measures similar to the ones evaluated here. The pain assessment tool most frequently used in the studies in the meta-analysis is the visual analogue scale [6,7,43,44]. Other pain assessment tools include the brief pain inventory [9,27], present pain intensity scale [8], and a 0 to 4 point ordinal scale [6]. Because of the limited number of studies identified in our literature search, any meaningful sub-analyses by dose regimen, patient demographics, or disease characteristics were precluded.
Thus, when using research results to guide zoledronate treatment, the findings of individual studies should be considered alongside the pooled estimates of treatment effect.

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Author Contributions

Min Zhu and Rui Liang contributed to the study concept and design. Min Zhu, Wei-Wei Zheng and Ling-Hui Pan performed literature searches and extracted data from eligible studies. Min Zhu performed all statistical analyses. Min Zhu, Rui Liang, Bing Huang, Ling-Hui Pan, Wei Qian, Jian-Hong Zhong, Wei-Wei Zheng, and Chang-Long Li drafted the manuscript.

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