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

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Abstract

目的: 一项混合治疗比较 (MTC) 被用来比较唑来膦酸、氯米芬、帕米膦酸和伊班膦酸 (静脉或口服) 在乳腺癌患者或前列腺癌患者腰椎相关事件 (SRE) 以及乳腺癌和前列腺癌以及多发性骨髓瘤患者中使用唑来膦酸的疗效。

实验设计: 在三种恶性肿瘤中进行双膦酸盐的系统性审查和SRE数据被提取。MTC的输出结果表明唑来膦酸的SRE率与唑来膦酸相比。

结果: 17项研究被识别 (7项乳腺癌, 3项前列腺癌, 7项多发性骨髓瘤)。数据可用于所有双膦酸盐在乳腺癌中存活; 但数据不可用于伊班膦酸 (口服或静脉) 在前列腺癌或对于口服伊班膦酸在多发性骨髓瘤中。在乳腺癌中唑来膦酸的SRE率在第一年中为1.60 (对于唑来膦酸), 1.67 (对于口服伊班膦酸 (SRE率, 4%) ), 1.70 (对于静脉伊班膦酸 (6%) ), 2.07 (对于帕米膦酸 (29%) ), 和2.29 (对于氯米芬 (42%) )。在前列腺癌中, SRE率在唑来膦酸为0.83, 氯米芬为1.11, 帕米膦酸为3.5, 和帕米膦酸为1.41 (对照率71%)。在多发性骨髓瘤中, SRE率在唑来膦酸为1.43, 氯米芬为1.64 (对照率15%), 1.90 (对照率33%), 和2.49 (对于口服伊班膦酸 (75%) )。

结论: 唑来膦酸似乎是对减少SRE风险最有效的双膦酸盐。在患者中增加乳腺癌或前列腺癌或多发性骨髓瘤。引用: Palmieri C et al. A Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool; 2Liverpool and Merseyside Breast Academic Unit, The Linda McCartney Centre, Royal Liverpool University Hospital, Liverpool; 3Academic Department of Medical Oncology, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral; 4Fullarton Consultancy, Sandy, Bedfordshire; and 5Academic Unit of Clinical Oncology, University of Sheffield, West York Park Hospital, Sheffield, United Kingdom

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

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

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

We undertook a MTC meta-analysis to investigate and compare the efficacy of zoledronic acid, clodronate, pamidronate, and ibandronate (i.e. and oral). Because most data for bisphosphonates come from trials in breast cancer, prostate cancer, and multiple myeloma, the MTC was limited to these three malignancies. Although it is recognized that the RANK ligand inhibitor, denosumab, has provided an additional option for the prevention of SREs in patients with bone metastases secondary to breast, prostate, and other solid tumors (27–30), the focus of this review was to provide further comparative information on the individual bisphosphonates.

Materials and Methods

Literature search and selection of studies

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

Data extraction

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

Data homogeneity

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

MTC meta-analysis

MTC meta-analysis, which uses Bayesian statistics, is distinct from traditional (“frequentist”) methods (e.g., risk ratios), having different underlying principles and assumptions, and providing a distinctly different output. An MTC uses a methodology for analyzing the probability of differential performance between treatments, whereas frequentist approaches provide a probability (P value) of whether the performances of treatments are the same or not. As such, the results of an MTC are not expressed as a P value,
although they can be considered similar/analogueous. It can also be argued that, for comparison purposes, the likelihood or probability measured by MTC gives a more practical estimate of relative treatment performance than a traditional P value. Some advantages of the Bayesian MTC approach include the following:

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

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

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

**Results**

**Overview of studies**

A total of 17 publications covering 20 RCTs were identified for inclusion in the MTC for the three malignancies (Tables 1–3). With the exception of studies comparing bisphosphonates [zoledronic acid vs. pamidronate (15) and oral ibandronate (16) in breast cancer and zoledronic acid versus clodronate (17) in multiple myeloma], all studies compared a bisphosphonate with placebo. In total, seven studies investigated zoledronic acid (4 mg every 3–4 weeks, i.v.; refs. 15–17, 33–36), five pamidronate (60/90 mg every 3–4 weeks, i.v.; refs. 15, 37–40), four clodronate (1,600–2,400 mg daily, orally; refs. 17, 41–43), two i.v. ibandronate (6 mg every 3–4 weeks; refs. 44, 45), and two oral ibandronate (50 mg daily; refs. 16, 46). Of the 14 placebo-controlled studies, 13 showed that bisphosphonates were efficacious in reducing the incidence of SREs in breast cancer; prostate cancer and multiple myeloma; Small and colleagues (38) did not demonstrate any advantage for pamidronate over placebo in preventing SREs in prostate cancer [patients affected by SREs: 42/169 (24.9%) vs. 46/181 (25.4%), respectively; not significant].

**Breast cancer**

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

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

**Prostate cancer**

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

The MTC showed that the annual incidence rate of SREs was lowest for zoledronic acid (0.83), followed by clodronate (1.11) and pamidronate (1.41; Table 5). The SRE rate for pamidronate was similar to that for placebo (1.41 vs. 1.47, respectively). Excess SRE rates over zoledronic acid for clodronate and pamidronate were 35% and 71%, respectively.
Table 1. Studies of bisphosphonates in breast cancer eligible for inclusion in the MTC meta-analysis

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

Abbreviation: NR, not reported.

aMean age.
bHypercalcemia was recorded but not included in annual incidence rate of SREs.
cCombined analysis of two RCTs.
dMedian time from any metastases to study entry.
eSignificantly more bone-only disease at baseline in placebo vs. clodronate arm (P < 0.05).
fPrior history of (vertebral) fractures.
gTrial also includes a 2-mg arm (6 mg is the licensed dose for SREs).
Multiple myeloma

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

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

Discussion

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

Within the MTC, the excess SRE rates for pamidronate, clodronate, and ibandronate (oral and i.v.) over zoledronic acid ranged from 4% to 42% in breast cancer, 35% to 71% in prostate cancer, and 15% to 75% in multiple myeloma. Exclusion of the study by Kohno and colleagues (36) resulted in greater excess SRE rates for the other bisphosphonates over zoledronic acid in breast cancer, with the remaining studies perhaps more reflective of the clinical situation in Western populations (excess SRE rate minus Kohno, 22%–72%). The apparently increased efficacy of
Table 3. Studies of bisphosphonates in multiple myeloma eligible for inclusion in the MTC meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators (regimen)</th>
<th>Patients (n)</th>
<th>Median age (range)</th>
<th>Stage (%)</th>
<th>Myeloma subtype (%)</th>
<th>Prior history of SREs (%)</th>
<th>Included SREs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan et al. (17)</td>
<td>Zoledronic acid (4 mg every 3–4 wks)</td>
<td>981</td>
<td>I, 59 (31–74)</td>
<td>I, 23; II, 36; III, 31; NA, 10</td>
<td>NR</td>
<td>27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pathologic fracture, spinal compression, radiotherapy and surgery to bone, new osteolytic lesion</td>
</tr>
<tr>
<td></td>
<td>Clodronate (1,800 mg daily)</td>
<td>979</td>
<td>I, 59 (39–89)</td>
<td>I, 15; II, 33; III, 41; NA, 12</td>
<td></td>
<td>30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>New osteolytic lesion, progression of previous bone lesion, pathologic fracture, radiotherapy to bone</td>
</tr>
<tr>
<td>Avilés et al. (34)</td>
<td>Zoledronic acid (4 mg every 4 wks)</td>
<td>46</td>
<td>67&lt;sup&gt;b&lt;/sup&gt; (43–75)</td>
<td>Illa, 100</td>
<td>lgG, 62; lgA, 20; light-chain, 11; nonsecretor, 4</td>
<td>Presense of ≥1 lytic lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clodronate (4 mg every 4 wks)</td>
<td>979</td>
<td>I, 59 (39–78)</td>
<td>I, 26; II, 33; Ill, 30; NA, 10</td>
<td></td>
<td>31&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Musto et al. (35)</td>
<td>Zoledronic acid (4 mg every 4 wks)</td>
<td>81</td>
<td>66 (41–82)</td>
<td>I, 100</td>
<td>lgG, 72; lgA, 28</td>
<td>No evidence of bone disease</td>
<td>Pathologic fracture, new osteolytic lesion, hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Clodronate (4 mg daily)</td>
<td>82</td>
<td>67 (42–84)</td>
<td>I, 100</td>
<td>IgG, 74; lgA, 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenson et al. (39)</td>
<td>Pamidronate (90 mg every 4 wks)</td>
<td>198</td>
<td>64&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Illa, 100</td>
<td>lgG, 57; lgA, 14; light-chain, 21; other&lt;sup&gt;f&lt;/sup&gt;, 8</td>
<td>Presense of ≥1 lytic lesion</td>
<td>Pathologic fracture, spinal cord compression, radiotherapy and surgery to bone, hypercalcemia</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>179</td>
<td>63&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ill, 100</td>
<td>lgG, 46; lgA, 24; light-chain, 26; other&lt;sup&gt;f&lt;/sup&gt;, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musto et al. (40)</td>
<td>Pamidronate (60 mg every 3–4 wks)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>45</td>
<td>67 (47–79)</td>
<td>I, 76</td>
<td>lgG, 80; lgA, 18; lgD, 2</td>
<td>No bone pain, bone lesions or hypercalcemia</td>
<td>Pathologic fracture, number and progression of osteolytic lesions, hypercalcemia</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>45</td>
<td>68 (45–80)</td>
<td>I, 71</td>
<td>lgG, 78; lgA, 22; lgD, 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lahtinen et al. (43)</td>
<td>Clodronate (2,400 mg daily)</td>
<td>168</td>
<td>&lt;65, 51&lt;sup&gt;e&lt;/sup&gt;; 65–74, 35%</td>
<td>IIa, 18; IIla,80</td>
<td>IgG, 54; lgA, 23; light-chain, 15; other&lt;sup&gt;f&lt;/sup&gt;, 8</td>
<td>0.53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pathologic fracture, number and progression of osteolytic lesions</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>168</td>
<td>NR&lt;sup&gt;f&lt;/sup&gt;</td>
<td>IIa, 15; IIla,84</td>
<td>lgG, 57; lgA, 24; light-chain, 17; other&lt;sup&gt;f&lt;/sup&gt;, 2</td>
<td>1–4, 42&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Menssen et al. (45)</td>
<td>i.v. ibandronate&lt;sup&gt;g&lt;/sup&gt; (2 mg every 4 wks)</td>
<td>99</td>
<td>83&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Illa,18; IIla,80</td>
<td>IgG, 54; lgA, 23; light-chain, 15; other&lt;sup&gt;f&lt;/sup&gt;, 8</td>
<td>0.55&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pathologic fracture, radiotherapy and surgery to bone, hypercalcemia, significant vertebral reduction (≥25%), severe bone pain (opiate treatment)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>99</td>
<td>83&lt;sup&gt;e&lt;/sup&gt;</td>
<td>IIa,15; IIla,84</td>
<td>lgG, 57; lgA, 24; light-chain, 17; other&lt;sup&gt;f&lt;/sup&gt;, 2</td>
<td>1–4, 39&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<sup>b</sup>Mean age.

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

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

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

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

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

<sup>h</sup> Observation without bisphosphonate.
zoledronic acid over the other bisphosphonates may relate to it having the greatest potency, as observed in preclinical studies (20). Interestingly, however, whereas zoledronic acid remained the most efficacious in all three cancer types, the ranking of the other bisphosphonates varied depending on the malignancy in question. In breast cancer, ibandronate (oral and i.v.) seemed to be the second most efficacious bisphosphonate, followed by pamidronate, then clodronate. In prostate cancer, however, clodronate seemed more effective than pamidronate, which performed little better than placebo (SRE rate, 1.41 vs. 1.47, respectively). Finally, in multiple myeloma, pamidronate was more efficacious than clodronate, with ibandronate (i.v.) having similar efficacy to placebo (SRE rate, 2.49 vs. 2.45, respectively). Only the results in breast cancer follow the relative potencies seen in preclinical studies (20). It could be hypothesized that the varying efficacy of ibandronate, clodronate, and pamidronate might be due in part to the differing underlying pathologies of the bone metastases from each malignancy: more osteoblastic lesions in prostate cancer,

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>Patients (n)</th>
<th>Annual incidence rate</th>
<th>Patients affected (follow-up duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosen et al. (15)</td>
<td>Zoledronic acid</td>
<td>139</td>
<td>0.91</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Pamidronate</td>
<td>140</td>
<td>1.57</td>
<td>–</td>
</tr>
<tr>
<td>Barrett-Lee et al. (16)</td>
<td>Zoledronic acid</td>
<td>672</td>
<td>0.42&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Oral ibandronate</td>
<td>654</td>
<td>0.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Kohno et al. (36)</td>
<td>Zoledronic acid</td>
<td>114</td>
<td>0.83</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>114</td>
<td>1.10</td>
<td>–</td>
</tr>
<tr>
<td>Lipton et al. (37)</td>
<td>Pamidronate</td>
<td>367</td>
<td>2.50</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>384</td>
<td>4.00</td>
<td>–</td>
</tr>
<tr>
<td>Paterson et al. (41)</td>
<td>Clodronate</td>
<td>85</td>
<td>2.19</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>88</td>
<td>3.05</td>
<td>–</td>
</tr>
<tr>
<td>Body et al. (44)</td>
<td>i.v. Ibandronate</td>
<td>154</td>
<td>1.76</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>158</td>
<td>3.34</td>
<td>–</td>
</tr>
<tr>
<td>Body et al. (46)</td>
<td>Oral ibandronate</td>
<td>287</td>
<td>0.76</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>277</td>
<td>1.39</td>
<td>–</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saad et al. (33)</td>
<td>Zoledronic acid</td>
<td>214</td>
<td>0.77</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>208</td>
<td>1.47</td>
<td>–</td>
</tr>
<tr>
<td>Small et al. (38)</td>
<td>Pamidronate</td>
<td>169</td>
<td>–</td>
<td>42 (27 wks)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>181</td>
<td>–</td>
<td>46 (27 wks)</td>
</tr>
<tr>
<td>Dearnaley et al. (42)</td>
<td>Clodronate</td>
<td>155</td>
<td>–</td>
<td>94 (median, 236 wks)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>156</td>
<td>–</td>
<td>103 (median, 236 wks)</td>
</tr>
<tr>
<td><strong>Multiple myeloma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgan et al. (17)</td>
<td>Zoledronic acid</td>
<td>981</td>
<td>0.33</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Clodronate</td>
<td>979</td>
<td>0.43</td>
<td>–</td>
</tr>
<tr>
<td>Avilés et al. (34)</td>
<td>Zoledronic acid</td>
<td>46</td>
<td>–</td>
<td>10 (median, 198 wks)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>48</td>
<td>–</td>
<td>23 (median, 198 wks)</td>
</tr>
<tr>
<td>Musto et al. (35)</td>
<td>Zoledronic acid</td>
<td>81</td>
<td>–</td>
<td>20 (median, 259 wks)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>82</td>
<td>–</td>
<td>29 (median, 259 wks)</td>
</tr>
<tr>
<td>Berenson et al. (39)</td>
<td>Pamidronate</td>
<td>198</td>
<td>1.3</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>179</td>
<td>2.2</td>
<td>–</td>
</tr>
<tr>
<td>Musto et al. (40)</td>
<td>Pamidronate</td>
<td>45</td>
<td>–</td>
<td>4 (median, 204 wks)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>45</td>
<td>–</td>
<td>9 (median, 204 wks)</td>
</tr>
<tr>
<td>Lahtinen et al. (43)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Clodronate</td>
<td>108</td>
<td>–</td>
<td>71 (104 wks)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>96</td>
<td>–</td>
<td>83 (104 wks)</td>
</tr>
<tr>
<td>Menssen et al. (45)</td>
<td>i.v. Ibandronate</td>
<td>99</td>
<td>2.13</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>99</td>
<td>2.05</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data estimated from figure in poster.

<sup>b</sup>Data taken from the Cochrane review (13).
more lytic lesions in multiple myeloma, and mixed lesions in breast cancer (2). It could equally be argued, however, that, overall, the breast cancer studies were more comparable in terms of patient populations and skeletal endpoints than was the case for the other two malignancies. The data in prostate cancer were relatively limited and included additional SREs not counted in the breast and myeloma studies (e.g., change of antineoplastic therapy to treat bone pain; refs. 33, 38). All of these considerations could have affected the ordering of bisphosphonates.

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

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

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Excess SRE rate (%)</th>
<th>Annual incidence rate</th>
<th>Excess SRE rate (%)</th>
<th>Annual incidence rate</th>
<th>Excess SRE rate (%)</th>
<th>Annual incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>1.60 (1.53)</td>
<td>—</td>
<td>0.83</td>
<td>—</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>2.29 (2.63)</td>
<td>35</td>
<td>1.11</td>
<td>33</td>
<td>1.90</td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>2.07 (2.41)</td>
<td>71</td>
<td>1.41</td>
<td>15</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>i.v. ibandronate</td>
<td>1.70 (1.98)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>75</td>
<td>2.49</td>
</tr>
<tr>
<td>Oral ibandronate</td>
<td>1.67 (1.87)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Placebo/control</td>
<td>3.30 (3.82)</td>
<td>78</td>
<td>1.47</td>
<td>72</td>
<td>2.45</td>
<td></td>
</tr>
</tbody>
</table>

*Values in parentheses are when Kohno et al. study (36) study (zoledronic acid vs. placebo) was removed from the MTC.*
denosumab (52), representing a new generation of bone
targeted agents, has further increased the therapeutic
options for oncologists in the treatment and prevention of
SREs in their patients. Ultimately, choice of therapy should
be made on an individual patient basis, taking into con-
sideration all of the earlier factors.

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

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C. Palmieri serves as a consultant/advisory board member for Novartis
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Analysis and interpretation of data (e.g., statistical analysis, biostatis-
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Writing, review, and/or revision of the manuscript: C. Palmieri, J.R.
Fullarton, J. Brown

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

Carlo Palmieri, John R. Fullarton and Janet Brown


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