Review

Bisphosphonates in breast cancer

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Breast cancer is the leading type of cancer among women, and bone metastases are common in patients with breast cancer, affecting more than half of all patients with advanced disease. Bisphosphonates are the current standard of care for preventing skeletal complications associated with bone metastases. Clinical trials investigating the benefit of bisphosphonate therapy have used a composite end point defined as a skeletal-related event (SRE) or bone event, which typically includes pathologic fracture, spinal cord compression, radiation or surgery to bone, and hypercalcaemia of malignancy. Bisphosphonates significantly reduced the incidence of these events. Zoledronic acid, pamidronate, clodronate and ibandronate have demonstrated efficacy compared with placebo. Zoledronic acid has also been compared with another active bisphosphonate (i.e. pamidronate) and shown by multiple event analysis to be significantly more effective at reducing the risk of SREs. Bisphosphonates effectively reduce and prevent skeletal complications in patients with bone metastases from breast cancer. Preclinical data suggest that bisphosphonates have antitumour effects. Bisphosphonates may also be of use in the adjuvant setting.

Key words: bisphosphonates, bone metastases, pamidronate, placebo, skeletal complications, zoledronic acid

Introduction

Breast cancer is a common invasive cancer that affects more than one million women annually worldwide, and bone metastases are frequent in patients with advanced metastatic disease [1–5]. Median survival for women with breast cancer is approximately 2 years after an initial diagnosis of bone metastases [1]. These patients, therefore, are at long-term risk for developing skeletal complications from bone metastases [6]. These skeletal complications include severe bone pain that may require strong narcotics or palliative radiation therapy, pathologic fracture, spinal cord or nerve root compression, and hypercalcaemia of malignancy (HCM). The resulting skeletal morbidity can substantially reduce quality of life [7]. Across all tumour types, patients with breast cancer have the highest incidence of skeletal complications [8–11]. In the placebo arms of two large phase III trials, after 2 years of follow-up, nearly 70% of patients had ≥1 skeletal complication, and approximately 50% had experienced a pathologic fracture [8]. These complications are the result of increased bone resorption that is characteristic of the bone lesions associated with malignant breast cancer. Therefore, therapies that effectively inhibit bone resorption can be expected to reduce the risk of skeletal complications.

Bisphosphonates for the treatment of bone metastases

Bisphosphonates have emerged in recent years as a highly effective therapeutic option for the prevention of skeletal complications secondary to bone metastases. Bisphosphonates bind preferentially to bone at sites of active bone metabolism and are released from the bone matrix during bone resorption. They are taken up by osteoclasts and potent inhibitors of osteoclast activity and survival, thereby reducing osteoclast-mediated bone resorption [12]. Newer nitrogen-containing bisphosphonates, such as zoledronic acid, pamidronate, and ibandronate, have a unique mechanism of action and increased clinical activity compared with first-generation bisphosphonates, such as etidronate and clodronate [13]. In particular, the nitrogen-containing bisphosphonates inhibit the mevalonate pathway of cholesterol biosynthesis in vitro and prevent protein prenylation in osteoclasts in vivo [13]. The post-translation modification or prenylation of small guanosine triphosphate-binding proteins, such as Ras, Rho and Rac, require two isoprenoid lipid intermediates: farnesyl diphosphate and geranylgeranyl diphosphate. Prevention of prenylation occurs when the enzyme farnesyl diphosphate synthase is inhibited, thus limiting production of farnesyl diphosphate and geranylgeranyl diphosphate, which then inhibits osteoclast activity.

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The nitrogen-containing bisphosphonates are more potent than first-generation compounds by several orders of magnitude and consequently can be safely administered via relatively short intravenous (i.v.) infusion and inhibit bone resorption at micromolar concentrations.

The clinical benefits of bisphosphonate therapy have been evaluated in a large number of clinical trials designed to capture data on skeletal complications (Table 1) [8, 14–23]. The majority of these trials have used a composite end point defined as a skeletal-related event (SRE) or bone event, which includes pathologic fracture, radiation therapy for bone pain or to treat or prevent a fracture, surgery to stabilize bone fractures, spinal cord compression and HCM. Such composite end points capture data on all clinically relevant events and are more likely to detect therapeutic benefits when treatment effects and disease morbidity are multifaceted [24].

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose and schedule</th>
<th>Trial</th>
<th>Primary efficacy end point</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate</td>
<td>1600 mg/day PO</td>
<td>Paterson et al. 1993 [14]</td>
<td>HCM, fractures, and radiotherapy</td>
<td>Significantly reduced the event rate for HCM, vertebral fractures, vertebral deformity, and the combined event rate for all events</td>
</tr>
<tr>
<td></td>
<td>800 mg/day PO</td>
<td>Kristensen et al. 1999 [15]</td>
<td>Time to first skeletal event, fractures, and radiotherapy</td>
<td>Reduced the number of bone events and significantly delayed the time to first bone event</td>
</tr>
<tr>
<td></td>
<td>1600 mg/day PO</td>
<td>Tubiana-Hulin et al. 2001[16]</td>
<td>Time to first skeletal event, fractures, and radiotherapy</td>
<td>Time to first bone event significantly delayed and significant reduced pain intensity and analgesic use</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>90 mg q 3–4 weeks i.v.</td>
<td>Hortobagyi et al. 1998 [17]</td>
<td>Percentage of patients with ≥1 SRE^a</td>
<td>Significantly reduced the incidence and delayed the onset of skeletal complications in patients receiving chemotherapy or hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>90 mg q 4 weeks i.v.</td>
<td>Theriault et al. 1999 [18]</td>
<td>HCM, fractures, spinal cord suppression, and radiotherapy</td>
<td>Reduced skeletal morbidity and significantly reduced the incidence and delayed the onset of skeletal complications in patients receiving chemotherapy or hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>90 mg q 3–4 weeks i.v.</td>
<td>Lipton et al. 2000 [8]</td>
<td>Pooled analysis [17, 18]</td>
<td>Showed significant reduction in the percentage of patients with ≥1 SRE, the median time to first SRE was extended by nearly 6 months, and a reduction in the mean skeletal morbidity rate was found</td>
</tr>
<tr>
<td></td>
<td>60 mg q 4 weeks i.v.</td>
<td>Hultborn et al. 1999 [20]</td>
<td>HCM, fractures, spinal cord compression, and radiotherapy</td>
<td>Significantly fewer SREs—defined as increased pain, HCM, pathologic fracture of long bones or pelvis, paralyses secondary to vertebral compression, palliative radiotherapy or surgery to bone, or change of antineoplastic therapy</td>
</tr>
<tr>
<td></td>
<td>45 mg q 3 weeks i.v.</td>
<td>Conte et al. 1996 [19]</td>
<td>Time to PD in bone</td>
<td>Effective in delaying the time to progression of bone lesions in 295 women</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>2 or 6 mg q 3–4 weeks i.v.</td>
<td>Body et al. 2003 [21]</td>
<td>SMPR</td>
<td>Significantly reduced the SMPR by 20% and extended the time to first SRE</td>
</tr>
<tr>
<td></td>
<td>50 mg/day PO</td>
<td>Body et al. 2004 [22]</td>
<td>SMPR</td>
<td>Significantly reduced the SMPR compared with placebo in a combined analysis</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4 mg q 4 weeks i.v.</td>
<td>Kohno et al. 2004 [23]</td>
<td>SRE rate ratio</td>
<td>Significant reduction in the rate of SREs. Reduced the percentage of patients with an SRE and delayed time to first SRE. Multiple event analysis demonstrated a 44% reduction in the risk of developing an SRE</td>
</tr>
</tbody>
</table>

PO = oral; HCM = hypercalcaemia of malignancy; q = every; SRE = skeletal-related event; PD = progressive disease; SMPR = skeletal morbidity period rate.

^aDefined as an SRE or bone event.
Using a composite definition of skeletal events, it is possible to assess treatment effect using a variety of outcome analyses. First-event analyses, such as proportion of patients with ≥1 SRE or time to first SRE, are objective and conservative end points that provide readily evaluable estimations of treatment effect. Of these, the US Food and Drug Administration has suggested that time to first event is the preferred end point because it also accounts for patients’ time on study [25]. However, first-event analyses capture information only about the first event and ignore data on all subsequent events that occur in any given patient. Skeletal morbidity rates or skeletal morbidity period rates (SMPR) assess the total number of events that occur during a designated time period (i.e. events/year). These analyses account for the occurrence of multiple skeletal events but assume that these events occur at a constant rate. However, clinical evidence suggests that patients with bone metastases exhibit considerable variation in both the number of skeletal events they experience and the rate at which these events occur [26]. Moreover, skeletal events do not demonstrate random distribution but often occur in clusters. Therefore, analyses that assume a linear event rate or random distribution (e.g. Poisson regression analysis) may overestimate treatment effects [27].

In contrast, multiple analyses account for non-constant event rates and are able to model all events and the time between events. Therefore, multiple event analyses are able to account for inter- and intrapatient variations in event rates and provide a statistically robust and comprehensive assessment of skeletal morbidity throughout the entire length of follow-up [28]. Andersen-Gill multiple event analysis calculates a hazard ratio that indicates the risk of skeletal events between two treatment groups. A hazard ratio <1 indicates a favourable treatment effect. Recently, non-parametric methods for multiple event analysis have also been described by Ghosh and Lin [29] and by Cook and Lawless [30]. These models calculate the cumulative incidence of skeletal complications and allow for right-censored data, thus accounting for death or study discontinuation for other reasons. Collectively, both first-event and multiple-event statistical analyses provide sensitive and comprehensive assessments of the clinical benefit of bisphosphonates in patients with bone metastases.

Bisphosphonates approved for the treatment of bone metastases from breast cancer

Several bisphosphonates (both oral and i.v.) have been approved for the treatment of patients with bone metastases from breast cancer in the United States and Europe (Table 1). The more potent nitrogen-containing bisphosphonates are administered i.v. and include 4 mg zoledronic acid (via 15 min infusion), 90 mg pamidronate (via 2 h infusion), and 6 mg ibandronate (1–2 h infusion). Only i.v. pamidronate and zoledronic acid have been approved in the USA and are thus recommended by the American Society of Clinical Oncology (ASCO) for the treatment of breast cancer patients with bone metastases [31]. Intravenous (6 mg) and oral ibandronate (50 mg/day) and oral clodronate (1600 mg/day) have been approved in Europe in patients with breast cancer and bone metastases [32].

**Oral clodronate**

The safety and efficacy of oral clodronate (1600 mg/day) were evaluated in a double-blind, placebo-controlled trial that enrolled 173 patients (Table 2) [14, 33]. This study assessed the number of HCM episodes, courses of radiotherapy to bone, and pathologic fractures (expressed as events per 100 patient-years). After a median follow-up of approximately 14 months, there was no statistical difference between treatment groups in the percentage of patients with either HCM, radiotherapy to bone, or fractures. In contrast, clodronate compared with placebo significantly reduced the event rate for HCM ($P<$0.01), vertebral fractures ($P<$0.025), vertebral deformity ($P<$0.001), and the combined event rate for all events (218.6 versus 304.8 events per 100 patient-years; $P<$0.001). However, the statistical methodology used in this trial has been criticised because of the potential for overestimation of treatment effects [34]. This is a particular concern given that the majority of patients died before they completed the 18-month study. Time to first SRE was later updated by Pavlakis and Stockler [33] based on an analysis of 185 patients. In the updated analysis, time to first bone event was significantly delayed (9.9 months for the clodronate group versus 4.9 months for placebo; $P=0.022$).

Two other placebo-controlled trials of oral clodronate have also been published. In the study by Kristensen et al. [15], 100 patients were randomised to receive clodronate (800 mg/day) or placebo in addition to chemotherapy and/or endocrine therapy for 2 years. Among 99 evaluable patients, clodronate reduced the number of bone events (defined as HCM, fractures or radiotherapy) and significantly delayed the time to first bone event compared with placebo ($P=0.015$). There were also significantly fewer fractures among patients treated with clodronate ($P=0.023$). However, the incidence of radiotherapy was higher after 15 months in the clodronate group ($P=0.069$). There was no effect of clodronate on

<table>
<thead>
<tr>
<th>Table 2. Efficacy of oral clodronate$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical end point</td>
</tr>
<tr>
<td>Mean SMR, events/100 patient-years</td>
</tr>
<tr>
<td>Vertebral fractures/100 patient-years</td>
</tr>
<tr>
<td>Vertebral deformity/100 patient-years</td>
</tr>
<tr>
<td>Median time to first SRE (n = 185), months$^b$</td>
</tr>
</tbody>
</table>

SMR = skeletal morbidity rate; SRE = skeletal-related event.

$^a$Defined as SRE or bone event; clinical outcome assessed after 18 months.

$^b$Based on updated analysis reported by Pavlakis et al. [33]
progression of bone disease or survival. Most recently, Tubiana-Hulin et al. [16] reported a study in 144 patients who were treated with either 1600 mg/day oral clodronate (n = 73) or placebo (n = 71) for up to 12 months. In this study, bone events were defined as HCM, radiotherapy to bone, pathologic fractures (including spinal cord compression), increase or onset of bone pain, or death due to bone metastases. Among 137 evaluable patients, the median time to first bone event was significantly delayed in the clodronate group (244 days versus 180 days for placebo; P = 0.05), and patients treated with clodronate had significant reductions in pain intensity and analgesic use compared with placebo (P = 0.01 and P = 0.02, respectively). These studies demonstrated that clodronate significantly reduces and delays skeletal morbidity in patients with bone metastases.

**Intravenous pamidronate**

The efficacy and safety of i.v. pamidronate (90 mg via 2 h infusion every 3–4 weeks) for the treatment of bone metastases secondary to breast cancer was established in the mid 1990s based on two large multicentre, randomised, placebo-controlled trials involving 754 patients [17, 18]. These trials each individually showed that pamidronate significantly reduced the incidence and delayed the onset of SREs—defined as pathologic fractures, spinal cord compression, surgery to treat or prevent fractures, HCM, and need for radiation to bone—compared with placebo [17, 18]. In the study reported by Hortobagyi et al. [17], pamidronate delayed SREs for up to 24 months in patients with breast carcinoma and osteolytic lesions receiving chemotherapy. Likewise, in the study reported by Theriault et al. [18], pamidronate significantly delayed and reduced SREs in patients receiving hormonal therapy. A pooled analysis of these trials at 2 years follow-up demonstrated that pamidronate significantly reduced the percentage of patients with ≥1 SRE (51% versus 64% for placebo; P < 0.001), extended the median time to first SRE by nearly 6 months (12.7 versus 7.0 months for placebo; P < 0.001), and reduced the mean skeletal morbidity rate (2.5 versus 4.0 SREs/year for placebo; P < 0.001; Table 3) [8].

<table>
<thead>
<tr>
<th>Clinical end point</th>
<th>Pamidronate, 90 mg (n = 367)</th>
<th>Placebo, n = 384</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 SRE†, %</td>
<td>51</td>
<td>64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median time to first SRE†, months</td>
<td>12.7</td>
<td>7.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean SMR, events/year</td>
<td>2.5</td>
<td>4.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bone lesion response, % (complete response and partial response)</td>
<td>32</td>
<td>22</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−0.07</td>
<td>+1.14</td>
<td>0.015</td>
</tr>
</tbody>
</table>

IV = Intravenous; SRE = Skeletal-related event; SMR = Skeletal morbidity rate.

*Excluding hypercalcemia of malignancy.

**Pamidronate also significantly improved bone lesion response (32% versus 22% for placebo; P = 0.002) and significantly reduced pain scores (P = 0.015) compared with placebo. Given these results, which are based on conservative clinical end points, i.v. pamidronate quickly became established as the international standard of care for women with bone metastases from breast cancer.**

These results were later confirmed in a study reported by Hultborn et al. [20] Among 404 women with bone metastases from breast cancer, patients treated with 60 mg pamidronate i.v. every 4 weeks had significantly fewer SREs—defined as increased pain, HCM, pathologic fracture of long bones or pelvis, paralyses secondary to vertebral compression, palliative radiotherapy or surgery to bone, or change of antineoplastic therapy—compared with placebo (P < 0.01). Patients treated with pamidronate also had delayed time to increase of pain (P < 0.01), decreased incidence of HCM (P < 0.05), and improved performance status compared with placebo (P < 0.05).

Pamidronate has also been shown to be effective in delaying the time to progression of bone lesions in 295 women treated with either 45 mg pamidronate or placebo via 1 h infusion every 3 weeks (median, 249 days versus 168 days for placebo; P = 0.02) [19]. This study also showed that significantly more patients treated with pamidronate reported decreased pain (44% versus 30% for placebo; P = 0.025). Skeletal-related events were not assessed in this study.

**Intravenous zoledronic acid**

Zoledronic acid has been compared directly with pamidronate and was shown by multiple-event analysis to be significantly more effective at reducing the risk of SREs among breast cancer patients (Table 4) [35–37]. Zoledronic acid reduced the risk of developing an SRE by an additional 20% over that achieved with pamidronate (P = 0.025) and by an additional 30% in patients receiving hormonal therapy (P < 0.01).

More recently, zoledronic acid (4 mg via 15 min infusion every 4 weeks for 1 year) has been compared with placebo in a study reported by Major et al. [36]. Zoledronic acid significantly reduced skeletal morbidity and delayed the time to first SRE (P < 0.001). Zoledronic acid also significantly reduced the incidence of HCM (P = 0.015) and improved pain scores (P < 0.05), and patients treated with zoledronic acid had significantly increased survival (median 137 versus 121 days; P = 0.025) compared with placebo. Similarly, patients treated with zoledronic acid reported improved quality of life (P < 0.001) and had significantly delayed time to increase of pain (P < 0.01) compared with placebo.

**Table 4. IV Zoledronic acid versus IV pamidronate in patients with breast cancer**

<table>
<thead>
<tr>
<th>Clinical end point</th>
<th>Zoledronic acid, 4 mg (n = 377)</th>
<th>Pamidronate, 90 mg (n = 389)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an SRE*, %</td>
<td>46</td>
<td>49</td>
<td>0.189</td>
</tr>
<tr>
<td>Median time to first SRE†, days</td>
<td>376</td>
<td>366</td>
<td>0.186</td>
</tr>
<tr>
<td>Skeletal morbidity rate</td>
<td>0.91</td>
<td>1.57</td>
<td>0.102</td>
</tr>
<tr>
<td>Multiple event analysis (A-G)</td>
<td>20% decreased risk</td>
<td>–</td>
<td>0.025</td>
</tr>
<tr>
<td>Survival-adjusted cumulative incidence of SRE†</td>
<td>–</td>
<td>–</td>
<td>0.046</td>
</tr>
</tbody>
</table>

IV = Intravenous; SRE = Skeletal-related event; SMR = Skeletal morbidity rate.

*Excluding hypercalcemia of malignancy.

†Data from Major et al. [36].

Data from Rosen et al. [35].
227 Japanese women with bone metastases from breast cancer (Table 5) [23]. Similar to the pamidronate trials, patients enrolled in this trial had predominantly osteolytic lesions. In this trial, the primary end point was the SRE rate ratio adjusted for history of pathologic fractures before study entry, which showed a significant 39% reduction in the rate of SREs for patients treated with zoledronic acid compared with placebo (ratio = 0.61; \( P = 0.027 \)). Secondary efficacy analyses demonstrated that zoledronic acid significantly reduced the percentage of patients with \( \geq 1 \) SRE (31% versus 52% for placebo; \( P = 0.001 \)) and delayed the time to first SRE (median not reached versus 360 days for placebo; \( P = 0.004 \)). Multiple-event analysis demonstrated a 44% reduction in the risk of developing an SRE (hazard ratio = 0.56; \( P = 0.009 \)) compared with placebo. Zoledronic acid also consistently reduced Brief Pain Inventory scores from baseline in this study. At every time point, patients in the placebo group had either no change or an increase from baseline in their median pain score, whereas patients in the zoledronic acid group had a decrease from baseline in their median pain score at every time point.

### Intravenous and oral ibandronate

Most recently, ibandronate (both oral and i.v.) has been evaluated for the prevention of skeletal complications in placebo-controlled trials of breast cancer patients with bone metastases (Table 6) [21, 22, 38]. A randomised, placebo-controlled trial of 2 or 6 mg i.v. ibandronate (via 1–2 h infusion every 3–4 weeks for up to 2 years) was conducted in 466 patients [21]. The primary efficacy end point was the SMPR, defined as the number of 12-week periods on study in which a patient experienced a new bone event divided by the number of periods on study. Bone events were defined as pathologic fracture, radiotherapy to treat bone pain or impending fracture, or surgery for bone complications. At 2 years, 6 mg ibandronate significantly reduced the SMPR by 20% (1.19 versus 1.48 events per patient-year for placebo; \( P = 0.004 \)) and extended the time to first SRE (median, 51 versus 33 weeks for placebo; \( P = 0.018 \)) compared with placebo [21]. Ibandronate (6 mg) reduced the percentage of patients with \( \geq 1 \) new bone event (51% versus 62% for placebo), but this difference did not reach statistical significance (\( P = 0.052 \)). Ibandronate (2 mg) demonstrated no significant clinical benefit.

Oral ibandronate (50 mg/day for up to 96 weeks) was also shown to reduce significantly the SMPR compared with placebo (0.95 versus 1.18 events per patient-year; \( P = 0.004 \)) in a combined analysis of two trials involving 564 patients with bone metastases [22]. This analysis excluded SREs that

### Table 5. Efficacy of zoledronic acid

<table>
<thead>
<tr>
<th>Clinical end point</th>
<th>Zoledronic acid, 4 mg (n = 114)</th>
<th>Placebo (n = 113)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRE rate ratio*</td>
<td>0.61†</td>
<td>–</td>
<td>0.027†</td>
</tr>
<tr>
<td>Patients with ( \geq 1 ) SRE, %</td>
<td>31</td>
<td>52</td>
<td>0.001</td>
</tr>
<tr>
<td>Median time to SRE, days</td>
<td>NR</td>
<td>360</td>
<td>0.004</td>
</tr>
<tr>
<td>Multiple event analysis risk ratio (range)</td>
<td>0.56 (0.363 to 0.867)</td>
<td>–</td>
<td>0.009</td>
</tr>
</tbody>
</table>

SRE = Skeletal-related event; NR = Not reached.

*Excluding hypercalcaemia of malignancy and adjusting for patients’ history of pathologic fractures before study entry.

†Permutation test.

Data from Kohno et al. [23].

### Table 6. Efficacy of IV and oral ibandronate

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical end point</th>
<th>Ibandronate (n = 154)</th>
<th>Placebo (n = 158)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ibandronate (6 mg)</td>
<td>Body et al. [21]</td>
<td>Patients with new bone event, %</td>
<td>51</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time to new bone event, months</td>
<td>11.8</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean SMPR†</td>
<td>1.19</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson regression, risk ratio</td>
<td>0.6</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical end point</td>
<td>Ibandronate (n = 287)</td>
<td>Placebo (n = 277)</td>
</tr>
<tr>
<td>Oral Ibandronate (50 mg/day)</td>
<td>Body et al. [22, 37]</td>
<td>Patients with new bone event, %</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time to new bone event, months</td>
<td>21.0</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean SMPR*</td>
<td>0.95</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson regression, risk ratio†</td>
<td>0.62</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in SRE, posthoc multiple event analysis (A-G)</td>
<td>38%</td>
<td>–</td>
</tr>
</tbody>
</table>

IV = Intravenous; SMPR = Skeletal morbidity period rate; SRE = Skeletal-related event; A-G = Andersen-Gill.

*Clinical outcome assessed after 24 months.

†Excluding hypercalcaemia of malignancy.
occurred during the first 3 months of study and included SREs that occurred following completion/withdrawal from the study. However, oral ibandronate did not significantly reduce the percentage of patients with a new bone event (45% versus 52% for placebo; \( P = 0.122 \)) nor did it significantly extend the time to first new bone event (median, 21 months versus 15 months for placebo; \( P = 0.089 \)). Based on these placebo-controlled trials, both oral and i.v. formulations of ibandronate (50 mg/day oral and 6 mg i.v.) have been approved in Europe for the treatment of breast cancer patients with bone metastases [32].

**Summary of clinical trials**

**Efficacy**

In patients with advanced breast cancer and bone metastases, the administration of oral or i.v. bisphosphonates in addition to chemotherapy and hormonal therapies reduces the risk of developing a skeletal event and also increases the time to development of SREs compared with placebo or no bisphosphonate [33]. Although all i.v. bisphosphonates have been shown to reduce the incidence of skeletal complications compared with placebo, only i.v. pamidronate and i.v. zoledronic acid have demonstrated statistically significant clinical benefit across multiple end points, especially the more conservative first-event analyses (Figure 1) [8, 21–23]. Zoledronic acid significantly reduced the rate, incidence and risk of SREs by approximately 40% compared with placebo. Pamidronate reduced the number of patients experiencing \( \geq 1 \) SRE by approximately 22% compared with placebo [8, 21–23], and oral or i.v. ibandronate reduced the percentage of patients with a new bone event by only 13% and 18%, respectively (Figure 1). However, zoledronic acid has been compared directly with pamidronate and was found significantly more effective at reducing the risk of SREs among breast cancer patients by an additional 20% over that achieved with pamidronate (\( P = 0.025 \)) [35, 36].

**Safety of intravenous and oral bisphosphonates**

In general, bisphosphonates are well tolerated. As a class, i.v. bisphosphonates are associated with acute-phase reactions in approximately 15%–20% of patients (primarily after the first one or two infusions), which are characterized by mild to moderate flu-like symptoms, such as low-grade fever, fatigue, arthralgia or myalgia, increased bone pain and nausea [39, 40]. Administration of i.v. bisphosphonates is also occasionally associated with mild imbalances in serum ions, such as calcium, magnesium and phosphorous [39]. Intravenous bisphosphonates can also have adverse effects on renal function. These effects are dependent on the dose and infusion rate, but are generally mild to moderate in severity (i.e. mild elevation of serum creatinine) and manageable. The incidence of severe renal adverse events is generally low. Among breast cancer patients treated with zoledronic acid for up to 2 years, <1% of patients developed grade 3 or 4 serum creatinine elevation [35].

**Effects on pain**

Several bisphosphonate trials have reported statistically significant improvements in pain compared with placebo [33], and bisphosphonates reduce the need for radiotherapy to bone, which serves as a surrogate for bone pain. In a systematic review of 25 randomised trials in metastatic breast cancer in which pain was evaluated, bisphosphonates generally had a beneficial effect [41]. The recent trial of zoledronic acid in Japanese women provides the most comprehensive evaluation of change from baseline score across time using the Brief Pain Inventory. Zoledronic acid consistently reduced bone pain from baseline at every monthly evaluation throughout the 12-month study [23]. Currently, however, there is insufficient evidence to recommend bisphosphonates as first-line therapy for the treatment of bone pain [42], and the American Society of Clinical Oncology guidelines recommend that the current standard of care for cancer pain should not be displaced by bisphosphonates [43]. Nevertheless, bisphosphonates are an important adjunct to analgesics and/or radiotherapy for the management of painful bone metastases.

**Quality-of-life benefits**

Bone pain and skeletal morbidity can lead to a rapid decline in a patient’s quality of life (QoL). Therefore, reducing skeletal complications and improving a patient’s QoL are intimately linked. Current data suggest that bisphosphonates can result in improvements in QoL or reduce declines in QoL in patients with metastatic breast cancer [41]. For example, a significant improvement in QoL was demonstrated for patients treated with 6 mg ibandronate for 96 weeks compared with placebo [44]. In a study by Weinfurt et al. [45], women receiving zoledronic acid or pamidronate for the prevention of SREs experienced an overall increase in health-related QoL scores. Collectively, these studies suggest that bisphosphonate therapy may have previously unappreciated benefits in terms of improved QoL during the course of treatment.
Effects on biochemical markers of bone metabolism

Bisphosphonates have profound effects on bone cell function that can be monitored using specific biochemical markers. In particular, markers of type 1 collagen breakdown have been evaluated in an attempt to both predict clinical outcome and identify a surrogate marker for individual patient benefit. Early small studies suggested a link between bone resorption rates and both pain relief [46] and the risk of fracture [47] during treatment with pamidronate. Subsequently, a larger study in bisphosphonate-naive patients demonstrated a rapid increase in the relative risk of an SRE in patients with elevation of the resorption marker, urinary n-telopeptide (NTX), suggesting it may be possible to identify a population of patients at increased risk for skeletal complications [48]. More recently, evidence from the large phase III trials of zoledronic acid has confirmed the relationship between bone resorption (as measured by urinary NTX) and skeletal morbidity, disease progression and death across a broad range of tumours affecting bone both with [49] and without [50] concomitant bisphosphonate treatment. The potential use of biochemical markers to refine the selection of patients for bisphosphonate treatments, and optimise both the schedule of administration and cost-effectiveness of bisphosphonate therapy is a current area of active research.

Antitumour effects of bisphosphonates

The activity of bisphosphonates in preventing bone metastases is an area of active investigation [51]. Preclinical studies suggest that bisphosphonates have direct antitumour effects in vitro and can reduce skeletal tumour burden and prevent the development of bone metastases in animal models [46]. Bisphosphonates have also demonstrated synergistic antitumour effects in combination with chemotherapy in breast cancer models [52]. Several clinical trials of oral clodronate and i.v. pamidronate also demonstrated that bisphosphonates can prevent bone metastases and may improve survival when used in the adjuvant setting. Long-term follow-up data from three trials of oral clodronate were recently reported. Of these, the most compelling data were those reported by Powles et al. [53]. In a large randomised, multicentre trial that had well-matched treatment arms, clodronate (1600 mg/day) significantly reduced the risk of bone metastasis during the 2-year treatment period (P = 0.031) and across 5 years of follow-up (P = 0.024). There was also an improvement in overall survival with long-term follow-up (P = 0.041). Jaschke et al. [54] also reported long-term results of the Heidelberg study showing that oral clodronate (1600 mg/day) improved the overall survival of breast cancer patients with micrometastases. Based on this evidence and the potent antitumour activity of zoledronic acid in preclinical models, zoledronic acid is being investigated in the adjuvant setting to prevent metastases to bone [52]. The Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial (target N = 3300) is currently evaluating the effect of zoledronic acid on disease-free survival and incidence of bone metastases in patients receiving standard adjuvant therapy [52].

Strategies for cost effectiveness and economic implications of bisphosphonate treatment

Cancer therapy is often expensive and the efficient use of health care resources is a concern [55]. Therefore, the cost effectiveness of bisphosphonates has been an issue. However, answering this question necessitates having reliable data on the costs associated with skeletal complications. Two recent studies in patients with prostate cancer have examined the health care costs associated with SREs. McKiernan et al. [56] studied the economic impact of SREs in the USA by evaluating insurance claims from 1994 to 2002 and found that total medical care costs were $59,522 for patients with SREs versus $39,038 for patients with no SREs (a difference of $20,484). Likewise, a study by Groot et al. [57] in the Netherlands found that the average cost of SREs (6078 Euros/patient) accounted for nearly half of the total treatment costs directly attributed to SREs (13,053 Euros/patient). Estimates in breast cancer patients have also determined that SREs can increase average health care costs by approximately $52,000 per patient, although the majority of these costs were not directly attributed to specific SREs [58]. Therefore, treatment to prevent SREs may reduce total health care costs in addition to reducing pain and improving function in patients with metastatic disease. However, there have been few pharmacoeconomic analyses published.

A recent systematic review of the cost effectiveness of bisphosphonates for the treatment of SREs found no cost effectiveness analyses for HCM. However, based on expert opinion the review suggested that it is more cost effective to prevent HCM than to treat HCM because of the extended hospitalization time associated with the treatment [59]. Bisphosphonates are highly effective agents for the prevention of HCM and, therefore, could be expected to reduce these costs. Similarly, these analyses suggest that bisphosphonates appear to be more cost effective for the prevention of skeletal morbidity in breast cancer patients with bone metastases because these patients have a high incidence of SREs.

In conclusion, bisphosphonates clearly improve selected outcomes in women with metastatic breast cancer and appear to be cost effective. Further study is needed, given the complexities of cancer treatment, to assess comprehensively the cost effectiveness of bisphosphonates and to determine the best use of finite health care resources.

Conclusions

Bone metastases are common in patients with advanced breast cancer, and treatment of bone metastases remains an important health care problem. Bisphosphonates provide significant benefits to patients with bone metastases by decreasing skeletal complications and reducing bone pain. Several bisphosphonates, including oral clodronate, i.v. pamidronate, oral and i.v. ibandronate, and i.v. zoledronic acid, have demonstrated significant clinical benefits compared with placebo. However, i.v. pamidronate and i.v. zoledronic acid have demonstrated
the most consistent clinical benefit across multiple end points. Zoledronic acid has also been shown to be significantly more effective than pamidronate in reducing the risk of developing an SRE (by multiple event analysis) in a direct prospective comparison. The role of bisphosphonates in the treatment of malignant bone disease continues to expand, and new opportunities are being actively explored. For example, preclinical evidence suggests that bisphosphonates have antitumour effects. Bisphosphonates may also be able to prevent or delay the development of bone metastases in patients with early stage breast cancer. Clinical studies with oral clodronate and i.v. pamidronate have provided further evidence that bisphosphonates can inhibit metastasis to bone. Accordingly, trials to evaluate the efficacy of zoledronic acid in the adjuvant setting are ongoing.

References


