The Use of Bisphosphonates in Elderly Cancer Patients

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Key Words. Bone metastases • Clodronate • Ibandronate • Pamidronate • Zoledronic acid • Elderly

LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. Discuss the role of bisphosphonate therapy in the management of metastatic bone disease.
2. Describe the differences between individual bisphosphonates with regard to safety and route of administration.
3. List the reasons for including elderly patients in clinical trials of bisphosphonates for the management of metastatic bone disease.

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ABSTRACT
As life expectancy increases throughout the 21st century, the size of the elderly population will also expand. This will have a marked effect on the number of patients with cancer who are classified as elderly. Despite this, the design of most clinical studies of cancer therapies excludes those patients who are ≥70 years of age.

Bisphosphonates are an example of a cancer therapy that has not been examined in randomized clinical trials of elderly patients. These agents are used for the prevention of skeletal complications and the relief of bone pain in patients with bone metastases. When deciding which bisphosphonate to prescribe to an elderly patient, each drug should be considered on its individual merits. Examples of areas of concern with bisphosphonates in elderly patients include their relative renal safety profiles and propensity for osteonecrosis of the jaw. Another consideration when choosing the most appropriate formulation is the preferred method of administration (oral or i.v.), which may affect patient compliance with therapy.

As the use of bisphosphonates increases, the need for data on their use in elderly patients also becomes greater. Clinical trials of bisphosphonates in this patient population are currently under way, and their results are keenly awaited. The Oncologist 2007;12:62–71

INTRODUCTION
As the life expectancy of the general population has increased, the number of elderly patients with cancer has risen as well. This number is predicted to increase further throughout the 21st century. Estimates suggest that between one fifth and one quarter of the population in the Western world will be ≥65 years of age by the year 2020 [1]. As the majority of cancers and cancer-related deaths will occur in the elderly, there is a significant and growing need for effective and appropriate treatment for cancer in these patients.

Patient age presents a number of challenges when prescribing medications. Factors such as comorbid conditions, declining organ function, and general frailty can substantially limit the effectiveness of treatment. Furthermore, elderly patients may already be taking a number of concomitant prescription medications that are associated...
with drug-drug interactions, which can increase toxicity or reduce treatment efficacy. In particular, elderly patients with cancer may be taking several medications such as chemotherapy and supportive care agents at any one time.

If the patients have metastatic bone disease (MBD), these prescription medications may also include a bisphosphonate. These agents are regarded as the standard of care for bone metastases. Four bisphosphonates are currently used for the treatment of MBD: clodronate (Bonefos®, Schering AG, Berlin; and Ostac® and Loron®, F. Hoffmann-La Roche Ltd., Basel, Switzerland), pamidronate (Aredia®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation), and ibandronate (Bondronat®; F. Hoffmann-La Roche Ltd.). Although the benefits of these agents are well documented, no randomized trial has been conducted in elderly patients with MBD to date. Without these data, it is not possible to predict the exact effects of bisphosphonates in this population. Bisphosphonate safety profiles are also relevant; side effects such as renal toxicity and osteonecrosis of the jaw (ONJ) must be considered. This article reviews clinical data on bisphosphonates when used for the treatment of MBD and highlights characteristics of individual agents that have particular relevance when treating elderly patients.

BISPHOSPHONATES AND MBD

MBD is a common and significant complication of metastatic cancers. It occurs in up to 95% of patients with multiple myeloma (MM); 75% of patients with breast and prostate cancer; and 15%–40% of patients with lung, colon, or kidney cancers [2, 3]. Bone metastases are associated with a number of debilitating sequelae, including severe pain, pathologic fractures that may require palliative radiation therapy, and spinal cord compression. The most common events are pathologic fractures and the need for radiation therapy [4]. Bisphosphonates inhibit osteoclast-mediated bone resorption and thereby reduce the incidence of skeletal complications. Since elderly patients are at an increased risk of skeletal events due to osteoporosis or other age-related comorbidities, treatment with a bisphosphonate is important.

The four bisphosphonates currently used for the treatment of MBD are summarized in Table 1. Clodronate, the first bisphosphonate to be used for treating bone metastases, is approved for use in an oral formulation for the treatment of osteolytic lesions, hypercalcemia, and bone pain in patients with carcinoma of the breast or MM. Pamidronate, a nitrogen-containing, intravenously administered bisphosphonate, is indicated for bone pain and osteolytic lesions in patients with breast cancer or MM. More recently, two newer-generation bisphosphonates, i.v. zoledronic acid and ibandronate, have become available. Zoledronic acid is a double-nitrogen, cyclic bisphosphonate available as an i.v. formulation. It is approved for the prevention of skeletal complications in patients with MM or bone metastases secondary to any solid tumors. Ibandronate is a single-nitrogen bisphosphonate, available in both i.v. and oral formulations, which has been approved for the prevention of skeletal events in patients with bone metastases from breast cancer.

Clinical Trial Data: Efficacy

Analysis of skeletal-related events (SREs) is normally the primary endpoint used in clinical trials of bisphosphonates [5]. SREs encompass such complications as pathologic fractures, radiation therapy to bone, and spinal cord compression. Different SRE scoring methods have been used in the bisphosphonate trials. For example, trials of zoledronic acid and pamidronate used the mean skeletal morbidity rate (SMR; the number of SREs per patient divided by time on study). In contrast, trials of ibandronate used the skeletal morbidity period rate (SMPR; the number of 12-week periods with new skeletal complications divided by the number of periods on study). A useful secondary endpoint of SRE efficacy that has been used in the trials of zoledronic acid and ibandronate is the Andersen-Gill multiple-event analysis. This methodology provides a more comprehensive assessment of skeletal morbidity [4]. Other outcomes commonly examined in clinical trials of bisphosphonates include relief of metastatic bone pain and improvement in quality of life.

Clodronate

SREs

Clinical trials of oral clodronate established its efficacy in patients with breast cancer and MM more than 10 years ago [6, 7]. More recently, two large, randomized, placebo-controlled trials designed to assess the efficacy of oral clodronate in the prevention of SREs were conducted. In the first trial, 100 patients with metastatic breast cancer (median age, 53 years) received either oral clodronate (800 mg) twice daily for 2 years or placebo. Treatment with clodronate resulted in a significantly lower occurrence of fractures (p = .023) and a significantly longer time to first SRE compared with placebo (p = .015). However, the effect of clodronate decreased with time; the need for radiation therapy increased in the clodronate group after 15 months (p = .069) [8]. In the other trial, 144 patients with breast cancer and osteolytic
bone metastases (median age: clodronate, 57 years; placebo, 59.5 years) received either oral clodronate (1,600 mg/day) or placebo for 1 year. Median time to first bone event increased significantly with clodronate treatment ($p < 0.05$) [9].

**Bone Pain**

Oral clodronate appears to be less effective than i.v. pamidronate in reducing bone pain. This was demonstrated in a small ($n = 51$; age, ~60 years), comparative trial of oral clodronate (1,600 mg daily) versus i.v. pamidronate (90 mg monthly) [10]. More patients on pamidronate experienced symptomatic pain relief than did those on clodronate.

**Pamidronate**

**SREs**

Three trials established the efficacy of the recommended 90-mg dose of i.v. pamidronate in patients with breast cancer and bone metastases [11–14]. In a long-term efficacy and safety trial, patients with metastatic breast cancer and osteolytic bone lesions (age not provided in publication) were randomized to either pamidronate or placebo every 3–4 weeks for 2 years [11]. Significantly fewer patients on pamidronate reported any skeletal complication at 15, 18, 21, and 24 months compared with placebo ($p < .001$). Similarly, in a placebo-controlled trial of pamidronate in patients receiving hormonal treatment who had breast cancer and ≥1 lytic bone lesion (mean age: pamidronate, 60 years; placebo, 62 years), a significant reduction in SMR was observed at cycles 12, 18, and 24 [12]. Compared with placebo, the number of patients who experienced skeletal complications at 24 cycles was reduced significantly (56% vs. 67%; $p = .027$). In patients with advanced MM and ≥1 lytic lesion (age: pamidronate, 64 years; placebo, 63 years), a significantly lower proportion of patients who received nine cycles of pamidronate had any skeletal event compared with those on placebo (24% vs. 41%; $p < .001$) [13]. Furthermore, the clinical benefit of pamidronate was still significant after a preplanned 21 cycles of additional treatment [14].

**Bone Pain**

The effect of i.v. pamidronate on bone pain has been investigated in several randomized trials. In patients with breast cancer or MM, i.v. pamidronate (90 mg every 3 or 4 weeks) decreased pain scores [11, 12]. However, in a combined analysis of two placebo-controlled studies of men with prostate cancer (age, ~71.5 years), no significant/sustained differences in self-reported pain, analgesic use, or mobility were found between patients treated with pamidronate and those given placebo [15].

**Zoledronic Acid**

**SREs**

The efficacy of i.v. zoledronic acid (4 mg every 3 or 4 weeks) for the prevention of SREs has been demonstrated in a number of pivotal phase III trials involving patients with breast cancer, MM, hormone-refractory prostate can-

### Table 1. Bisphosphonates used for the treatment of metastatic bone disease

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Clodronate</th>
<th>Pamidronate</th>
<th>Zoledronic acid</th>
<th>Ibandronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing regimen</td>
<td>1,600 mg/day; range: 800–3,200 mg/day (maximum)</td>
<td>900 mg for 2–4 hours every 3–4 weeks</td>
<td>90 mg for &gt;2 hours every 3–4 weeks</td>
<td>4 mg for ≥15 minutes every 3–4 weeks in patients with creatinine clearance &gt;60 ml/min(^a)</td>
</tr>
<tr>
<td>Indication(^b)</td>
<td>MBD from breast cancer; multiple myeloma; all solid tumors; HCM</td>
<td>MBD from breast cancer; multiple myeloma; HCM</td>
<td>MBD from breast, prostate, lung, or other solid tumors; multiple myeloma; HCM</td>
<td>MBD from breast cancer; HCM</td>
</tr>
</tbody>
</table>
| Use of Bisphosphonates in Elderly Cancer Patients | 64 | by guest on September 6, 2017 | http://theoncologist.alphamedpress.org | Downloaded from | Use of Bisphosphonates in Elderly Cancer Patients | 64 | by guest on September 6, 2017 | http://theoncologist.alphamedpress.org | Downloaded from | b Only pamidronate and zoledronic acid are Food and Drug Administration-approved for use in the U.S.

Abbreviations: HCM, hypercalcemia of malignancy; MBD, metastatic bone disease.

\(^a\) For patients with reduced renal function, the dose of zoledronic acid should be adjusted [47, 48].

\(^b\) Only pamidronate and zoledronic acid are Food and Drug Administration-approved for use in the U.S.
cancer (HRPC), and other solid tumors [16–20]. Results from these trials are presented in Table 2.

In the pivotal noninferiority trial in patients with breast cancer and MM, i.v. zoledronic acid (4 mg infused every 3 or 4 weeks) showed comparable efficacy to i.v. pamidronate (90 mg) for the prevention of SREs [16, 17]. Results from a multiple-event analysis found a greater reduction in the risk for developing SREs with zoledronic acid than with pamidronate (risk ratio, 0.841; \( p = .03 \)) [17]. The effects of zoledronic acid therapy in patients with breast cancer were also evaluated in a Japanese placebo-controlled registration trial of patients with breast cancer [21]. The results showed that the SRE rate ratio at 1 year adjusted for history of prior fracture was significantly lower in the zoledronic acid group (39% reduction, \( p = .027 \)). According to multiple-event analysis, zoledronic acid reduced the risk of SREs by 41% (\( p = .019 \)).

In the phase III prostate cancer trial, significantly fewer patients on zoledronic acid experienced SREs compared with those on placebo [18]. Zoledronic acid reduced the risk for SREs by 36% (\( p = .002 \)) [19]. In the phase III trial in patients with solid tumors, although the primary endpoint (the number of patients with SREs at 9 months) was reduced in the zoledronic acid group, this did not reach statistical significance when compared with the placebo group. The risk of SREs was reduced by 27% with zoledronic acid (\( p = .017 \)) [20].

**Bone Pain**

In the comparative trial, both zoledronic acid (4 mg) and pamidronate (90 mg) resulted in decreases in pain scores at 12 months (~1-point decrease in Brief Pain Inventory composite pain scores compared with baseline). Use of analgesics either remained stable or decreased [17]. In the Japanese trial, zoledronic acid significantly reduced Brief Pain Inventory pain scores compared with baseline and placebo (no \( p \) value reported) [21]. The reduction of pain intensity was obtained 4 weeks after the first infusion of zoledronic acid. Similarly, patients with HRPC and bone metastases reported fewer increases in pain and analgesic scores with zoledronic acid than with placebo [18, 19]. In the solid tumor trial by Rosen et al., the mean composite pain score increased from baseline in the zoledronic acid and placebo groups, indicating increases in pain. However, the mean composite pain score was reduced in those patients on zoledronic acid who had pain at baseline [20]. The pain-relieving effects of i.v. zoledronic acid have also been demonstrated in three nonblinded studies in patients with MBD resulting from various primary malignancies [22–24]. Blinded studies confirming the pain efficacy of zoledronic acid are warranted.

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**Ibandronate**

**SREs**

Both i.v. and oral ibandronate have been evaluated for the prevention of SREs in patients with breast cancer and bone metastases (Table 3) [25–27]. The efficacy of i.v. ibandronate (6 mg via 1–2-hour infusions every 3 or 4 weeks) was demonstrated in a phase III, placebo-controlled trial of 312 patients with breast cancer [28]. After 2 years of treatment, patients treated with i.v. ibandronate (6 mg) had a significantly lower SMPR (\( p = .004 \)) than patients who received placebo. Andersen-Gill multiple-event analysis showed that i.v. ibandronate significantly reduced the risk for SREs by 29% (\( p = .0183 \)) [27]. Oral ibandronate (50 mg/day) was also effective in preventing SREs compared with placebo. In the combined analysis of two trials reported by Body et al. [29], oral ibandronate significantly reduced SMPR (\( p = .004 \)). Moreover, oral ibandronate was associated with a 38% lower risk for SREs than placebo (Andersen-Gill multiple-event analysis, \( p = .0183 \)) [27]. Similar results were obtained when risk reductions were calculated by Poisson regression method (i.v. ibandronate: 40%, \( p = .0033 \); oral ibandronate: 38%, \( p = .0001 \)) [25].

The comparative benefits of zoledronic acid and ibandronate in terms of SREs have yet to be established; however, one trial has assessed the ability of both drugs to reduce markers of bone turnover [30]. Bone markers are useful surrogates for bisphosphonate efficacy in MBD [5]. In the head-to-head trial, both oral ibandronate and i.v. zoledronic acid reduced levels of bone turnover markers to a similar extent. To confirm equal efficacy of both bisphosphonates, clinical trials are currently under way to directly compare zoledronic acid and oral ibandronate across SRE endpoints [31, 32].

**Bone Pain**

In the phase III trials, both formulations of ibandronate significantly reduced pain scores compared with baseline for up to 2 years [33, 26]. The maximal relief of bone pain was obtained after approximately 12 weeks of treatment with standard i.v. and oral ibandronate dosing. Analgesic use was lower only in the ibandronate treatment groups, reaching statistical significance for oral ibandronate (\( p = .019 \) vs. placebo) [33].

A number of small phase II studies suggest that intensive dosing schedules of ibandronate may achieve rapid pain relief within 3 days in patients with moderate-to-severe bone pain [33–36]. Two of the trials reported by Heidenreich et al. have assessed the effects of i.v. ibandronate as loading and maintenance dosing. In those trials, patients with prostate cancer (\( n = 25 \)) or urologic cancer (\( n = 53 \);
prostate, renal, or bladder cancer) received i.v. ibandronate (6 mg) on 3 consecutive days (the loading dose) followed by standard i.v. ibandronate therapy for 20 weeks (6 mg every 3–4 weeks). In the prostate cancer trial, 92% of patients experienced significantly reduced pain scores \((p < 0.001)\) \([34]\). Similarly, in the urologic cancer trial, 83% of patients experienced pain relief, with 25% of patients becoming pain-free. The reduction in pain scores was statistically significant at day 3 (from 7.5 at baseline to 3 at day 3) and remained below baseline during the maintenance phase \([35]\).

**Effects of Bisphosphonates on Quality of Life**

In total, eight trials have assessed improvements in the quality of life resulting from treatment with bisphosphonates. These have been reviewed in full in Pavlakis et al. \([37]\). Of these, only the pivotal ibandronate trials reported a statistically significant improvement compared with placebo. Diel and colleagues found a statistically significant difference in global functioning between i.v. ibandronate (6 mg) and placebo groups \((p = 0.004)\) \([33]\). Similarly, patients on oral ibandronate (50 mg) had a significantly better quality of life than those on placebo in the two oral trials \((p = 0.032)\) \([26]\).

**SAFETY OF BISPHOSPHONATES IN MBD**

Bisphosphonates can be used to treat bone metastases in elderly cancer patients, but age-related conditions and co-morbidities must be taken into consideration. For example, many elderly patients have age-related renal function impairment or renal insufficiency (creatinine clearance <60 ml/minute). These individuals may be at increased risk for renal toxicity if treated with certain i.v. bisphosphonates.

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**Table 2. Phase III studies of i.v. zoledronic acid for the prevention of SREs \([16, 17, 19, 21]\)**

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer and MM (25 months)</th>
<th>HRPC (24 months)</th>
<th>Lung/other solid tumors (9 months)</th>
<th>Breast cancer (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zoledronic acid (4 mg; (n = 561))</td>
<td>Pamidronate (90 mg; (n = 555))</td>
<td>Zoledronic acid (4 mg; (n = 214))</td>
<td>Placebo ((n = 208))</td>
</tr>
<tr>
<td>Age, median (years)</td>
<td>60</td>
<td>58.5</td>
<td>72</td>
<td>64</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>47</td>
<td>51</td>
<td>38</td>
<td>49, (p = .028)</td>
</tr>
<tr>
<td></td>
<td>(\geq 1) SRE (%) SRE rate ratio at 1 year</td>
<td>38</td>
<td>38</td>
<td>44, (p = .127)</td>
</tr>
<tr>
<td></td>
<td>(0.61) (p = .027)</td>
<td>(0.640) (p = .002)</td>
<td>(0.732) (p = .017)</td>
<td>(0.59) (p = .019)</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Multiple-event analysis, RRb</td>
<td>0.841, (p = .030)</td>
<td>0.640, (p = .002)</td>
<td>0.732, (p = .017)</td>
</tr>
<tr>
<td></td>
<td>(0.59) (p = .027)</td>
<td>(0.640) (p = .002)</td>
<td>(0.732) (p = .017)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Mean.

\(b\) Risk ratio versus placebo (Andersen-Gill model).

Abbreviations: HRPC, hormone-refractory prostate cancer; MM, multiple myeloma; RR, risk ratio; SRE, skeletal-related event.

**Table 3. Phase III studies of i.v. and oral ibandronate for the prevention of skeletal-related events in patients with breast cancer and bone metastases \([25–27]\)**

<table>
<thead>
<tr>
<th></th>
<th>i.v. ibandronate (6 mg)(a)</th>
<th>Placebo</th>
<th>Oral ibandronate (50 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td>(n = 154)</td>
<td>(n = 158)</td>
<td>(n = 287)</td>
<td>(n = 277)</td>
</tr>
<tr>
<td>Age, median (years)</td>
<td>56(b)</td>
<td>54.5(b)</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Primary endpoint SMPR</td>
<td>1.19</td>
<td>1.48, (p = .004)</td>
<td>0.95</td>
<td>1.18, (p = .004)</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Multiple-event analysis, RRc</td>
<td>0.71, (p = .0183)</td>
<td>0.62, (p = .0183)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Infused over 1–2 hours.

\(b\) Mean.

\(c\) Hazard ratio versus placebo (Andersen-Gill model).

Abbreviations: RR, risk ratio; SMPR, skeletal morbidity period rate.
Occasionally, the deterioration of renal function can be severe, resulting in acute renal failure, dialysis, and, in some cases, death [38]. Elderly patients may also have renal impairment as a result of their cancer. For example, renal failure is a major complication of MM [39], and bladder cancer can be associated with hydronephrosis [40]. Concomitant medications such as aminoglycoside antibiotics and some chemotherapy drugs (mainly cisplatin and, less extensively, its analogs) may also induce renal toxicity [41]. The administration of bisphosphonates via the i.v. route is also associated with transient acute-phase reactions, usually occurring after the first infusion [42]. Some oral dosing regimens are associated with upper gastrointestinal problems.

Clinical Trial Data

Clodronate
Noncompliance with oral clodronate therapy is often a result of the relatively high incidence of gastrointestinal adverse events associated with this bisphosphonate. In a 2-year trial of oral clodronate (1,600 mg/day) in patients with breast cancer, gastrointestinal adverse events were significantly more common in the clodronate group than in the placebo group (66% vs. 56%; \( p < .05 \)) [43].

Pamidronate
Long-term treatment with pamidronate in elderly patients (median age, 73 years; \( n = 22 \)) with bone metastases resulting from breast cancer, prostate cancer, or MM was found to be effective and well tolerated [44]. Adverse events of fever, nausea, and diarrhea were reported in 23%, 18%, and 14% of patients, respectively. There were two cases (9%) of reversible acute renal insufficiency. However, this was unexpected, because long-term pamidronate use is usually associated with deterioration in renal function [45].

Zoledronic Acid
Although zoledronic acid is well tolerated, renal toxicity appears to be more common with this agent than with any other bisphosphonate [45]. In the pivotal phase III trials, approximately 10%–15% of patients experienced renal impairment [16, 18, 20]. The incidence of renal dysfunction with zoledronic acid may be higher in routine clinical practice. For example, in a retrospective review of medical charts, 38% of patients with MM had renal impairment with zoledronic acid therapy [46]. As a result of concerns over the renal safety of zoledronic acid, the product labeling now mandates regular monitoring of renal function prior to each infusion, adequate hydration, and treatment discontinuation in the event of further deterioration in renal function [47, 48]. Dose reductions are also required in patients with mild or moderate renal impairment (creatinine clearance, 30 to >60 ml/minute).

Ibandronate
Unlike the other intravenously administered bisphosphonates, data suggest that the renal safety profile of ibandronate is similar to that of placebo. Using data from the pivotal i.v. trial, Body et al. conducted a post hoc Kaplan-Meier analysis of time to serum creatinine increase with ibandronate [49]. The definition for an increase in serum creatinine was identical to that used in the comparative trial of zoledronic acid and pamidronate [16, 17]. After 96 weeks of treatment, fewer patients on ibandronate had defined serum creatinine increases (6% vs. 12% with placebo, \( p = .22 \)). Furthermore, in a 2-year extension of the phase III trial, there were no clinically relevant renal adverse events, and in both groups, serum creatinine levels were similar for up to 4 years [50]. Intensive dosing with i.v. ibandronate does not appear to compromise renal safety, including in patients with urologic cancer and compensated renal insufficiency [51]. Few studies have investigated the efficacy of ibandronate in patients with MM [52, 53]. However, available data suggest that ibandronate is well tolerated in this indication, even in elderly patients with pre-existing renal failure [53, 54].

Because renal toxicity is not a concern with oral bisphosphonate therapy, the oral formulation of ibandronate may be a viable alternative for elderly patients who have renal safety issues using i.v. bisphosphonates. The pooled safety results from the two phase III trials demonstrated that oral ibandronate is well tolerated [29]. The incidence of mild treatment-related upper gastrointestinal adverse events was low (<7.0%) and only slightly higher in the ibandronate group than in the placebo group.

The acute-phase reactions and flu-like symptoms that can occur during the first 3 days following i.v. administration of bisphosphonates are likely to have a particularly detrimental effect in elderly patients and lead to increased incapacitation. In the comparative bone marker trial, fewer patients in the oral ibandronate group experienced adverse events than those in the zoledronic acid group. Importantly, there was a lower incidence of treatment-related pyrexia and flu-like symptoms during the first 3 days for oral ibandronate (2% vs. 27% with zoledronic acid) [30]. Similar results were obtained in a small 12-week study of i.v./oral ibandronate and i.v. zoledronic acid in 77 patients with breast cancer or MM. In that trial, patients in the ibandronate group received the i.v. formulation on day 1 (15-minute infusion) followed by oral ibandronate (50 mg) from day 2 onward. The incidence of pyrexia and flu-like
Symptoms experienced during days 1–3 was lower in the ibandronate group (13% vs. 26% with zoledronic acid) [55].

Osteonecrosis of the Jaw
In recent years, ONJ has emerged as a complication of bisphosphonate therapy [56–58]. Current reports suggest that bisphosphonates may vary in their propensity to cause ONJ. Zoledronic acid and pamidronate appear to be associated with a higher risk for ONJ compared with ibandronate [57]. In a review of medical records from 252 cancer patients, 17 (6.7%) developed ONJ. All occurrences of ONJ were diagnosed in patients who were treated with zoledronic acid alone (seven patients; 2.8%), after pamidronate (nine patients; 3.6%), or preceding ibandronate (one patient; 0.4%) [57]. Length of exposure to bisphosphonates appears to be the most important risk factor for occurrence [45]. Furthermore, dental procedures/use of dentures may increase the risk for ONJ. This is particularly relevant to elderly patients, since this population is more prone to dental problems than their younger counterparts.

Management Issues in Elderly Patients
Administration of bisphosphonates via the i.v. route may be more suitable for certain elderly cancer patients. Treatment can be combined with other drugs, such as chemotherapy, guaranteeing compliance; however, oral formulations do have a number of benefits. Oral bisphosphonates are not associated with adverse effects on renal function. Moreover, patients do not need to visit the hospital for their therapy, which is an important advantage for elderly patients who may have mobility problems and would prefer the convenience of at-home treatment. One of the main issues with oral administration is patient compliance, and this is particularly relevant in elderly patients. Oral clodronate tablets are large and difficult for some patients to swallow. In a study of clodronate in patients with metastatic bone pain (n = 55), 11% of patients discontinued treatment because of difficulty swallowing the capsules [59]. In contrast, oral ibandronate is a small tablet (approximately 1 cm in length) administered once daily. In the phase III and open-label extension trials, no patients withdrew due to difficulties with swallowing [29, 60]. In some countries, oral medications may not be reimbursed; this means that the cost of the drug needs to be paid out of the patients’ own pockets. Oral ibandronate is reimbursed in most European countries and other markets, with the exception of France, where oral ibandronate is not available.

Ibandronate Clinical Trials in the Elderly
As has been discussed, there are many issues associated with the effective treatment and supportive care of elderly cancer patients. However, a lack of evidence from clinical trials means that the specific needs and requirements of this population are not currently being addressed. The results from phase II studies indicate that loading-dose ibandronate achieves rapid pain relief in patients who have pain despite opioid use and radiation therapy. In an attempt to define more clearly the effects of bisphosphonate therapy in elderly patients with MBD, we have designed a randomized, 6-month, phase II study of the efficacy and safety of loading-dose ibandronate followed by i.v. or oral ibandronate maintenance therapy in 126 patients ≥70 years of age. The primary endpoint is the effect of ibandronate on bone pain. Secondary endpoints include improvements in quality of life and World Health Organization performance status score. Results are expected in January 2007. In Germany, a clinical study is evaluating the effects of adjuvant treatment with ibandronate with or without capecitabine in elderly patients (≥65 years of age) with early breast cancer. The primary endpoint is event-free survival.

Summary
The four bisphosphonates approved for use in patients with MBD have differing efficacy and safety profiles. Currently, there are no data from randomized clinical trials on the effects of bisphosphonates in elderly patients with cancer. There have been a number of clinical trials with bisphosphonates that have included substantial numbers of elderly patients, particularly in trials of multiple myeloma or prostate cancer patients [7, 15, 18, 19, 22, 23]. Safety results from these studies vary; a study of MM patients reported that safety of clodronate was comparable with that of placebo [7], whereas in a placebo-controlled study of zoledronic acid [18], there was a greater incidence of fatigue, anemia, myalgia, fever, and lower-limb edema (>5% more patients experiencing these adverse events), along with increased renal deterioration in the zoledronic acid groups. Until randomized head-to-head safety data in elderly patients become available, physicians will have to use what is known about the use of these agents in the general population to select the most appropriate bisphosphonate for this cohort of patients.

Clinical trials to assess the role of bisphosphonate therapy in other indications, for example, the adjuvant setting and in the prevention of cancer treatment-induced bone loss, are currently in progress. If successful, this may result in bisphosphonates being used in even more elderly patients with cancer. Such increased use raises concerns about the overall safety of bisphosphonates in elderly patients, whose
response to therapy may be affected by factors such as co-morbidity, decreased organ function, and polypharmacy. Specific safety precautions should be taken with regard to renal toxicity and ONJ, which are associated with the use of some bisphosphonates and are of particular concern when treating elderly patients.

There are also management issues associated with the use of these therapies, such as route of administration. Both oral and i.v. formulations are available, and an assessment should be made by the physician as to which is the most appropriate, based on the needs of the individual patient.

Awareness of the importance of including elderly patients in clinical trials is increasing. For example, one trial has recently been designed specifically to identify the effects of loading-dose ibandronate in patients ≥70 years of age. Metastatic bone pain accounts for a large part of the morbidity associated with skeletal metastases [61, 62]. Patients have decreased mobility and are often bedridden, ultimately experiencing poor quality of life. Since aging is generally associated with a loss of mobility, the effects of metastatic bone pain can have a substantial impact on the lives of elderly patients. The pain-relieving effects of loading-dose ibandronate may allow patients to resume activities of daily living and no longer be confined to the hospital/home. The results of the ibandronate trial are keenly awaited.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

C.G. has acted as a consultant for Roche, AstraZeneca, Eli Lilly, and Dompe Biotec.

**REFERENCES**

Use of Bisphosphonates in Elderly Cancer Patients


