Prolonged Efficacy of a Single Dose of the Bisphosphonate Zoledronic Acid

Janet E. Brown,1 Susan P. Ellis,1 James E. Lester,1 Sandra Gutcher,1 Tina Khanna,1 Om-Prakesh Purohit,1 Eugene McCloskey,2 and Robert E. Coleman1

Abstract

Purpose: Bisphosphonates play a central role in the management of bone loss due to a range of disorders, including metastatic bone disease, cancer treatment–induced bone loss, and postmenopausal osteoporosis. With potent bisphosphonates, such as zoledronic acid, it may be possible to maintain efficacy with relatively infrequent administration.

Experimental Design: Sixty-six patients who were osteopenic at >1 year following curative cancer therapy received a single i.v. 4 mg dose of the bisphosphonate zoledronic acid. Bone mineral density (BMD) was measured using double-beam X-ray absorptiometry scan and the bone resorption marker N-telopeptide of type II collagen was determined using a chemiluminescence ELISA assay.

Results: The single dose of zoledronic acid induced mean increases in bone BMD at the lumbar spine of 3.1%, 5.2%, and 5.3% and at the total hip of 2.7%, 3.5%, and 4.3% after 12, 24, and 36 months of follow-up, respectively (P < 0.001 at all time points). By 36 months, 84% of patients had achieved increase in BMD at the spine and 90% at the hip. The mean percentage decrease in the bone resorption marker N-telopeptide was —58% at 6 weeks and 42%, 33%, and 31% at 12, 24, and 36 months, respectively (P < 0.001).

Conclusions: A single dose of zoledronic acid in patients with low BMD results in a sustained increase in BMD and a corresponding decrease in bone resorption. Very infrequent administration of zoledronic acid may have clinical benefits in terms of convenience, reduced toxicity, improved compliance, and cost.

Bisphosphonates play a central role in the management of bone loss due to a range of disorders, including metastatic bone disease, cancer treatment–induced bone loss, Paget’s disease, and, notably, postmenopausal osteoporosis. Bisphosphonates are therefore very widely used, with many patients receiving continuous treatment for years and potentially decades. The drugs have proven benefit, not only in preventing bone loss but also in prevention of fragility fractures (1, 2).

Although generally well tolerated, bisphosphonates are not without associated problems, such as gastrointestinal toxicity, poor absorption, and suboptimal compliance of oral agents (3), as well as acute phase reactions and occasional nephrotoxicity with i.v. administration (4, 5). The occurrence of osteonecrosis of the jaw is also of growing concern, especially when nitrogen-containing bisphosphonates are given i.v., once every three to four weeks over a long period for metastatic bone disease (6–8). The clinical decision to use a bisphosphonate, especially over prolonged periods, must therefore be made with clear risk/benefit assessment. In recent years, development of the more potent nitrogen-containing bisphosphonates has led to the possibility of relatively infrequent dosing, with considerable potential benefits in compliance, efficacy, adverse event profile, convenience, and cost (9, 10).

There are increasing numbers of long-term cancer survivors who have received adjuvant chemotherapy and hormonal therapies. Initial attention has focused on treatment of the malignancy, but the possible long-term effects of such cancer treatments on the skeleton, with accelerated bone loss, which may lead to osteoporosis and fragility fractures, have been highlighted recently (11–15). In cancer treatment–induced bone loss, less frequent dosing with bisphosphonates is beginning to be explored. A study in 401 patients by Gnant et al. (16) showed that breast cancer patients receiving the severe potential insult to bone from concomitant ovarian suppression and an aromatase inhibitor experienced a bone mineral density (BMD) loss of 14.4% after 36 months (P < 0.001). By contrast, in patients receiving the same endocrine therapy with 6 monthly zoledronic acid, BMD remained stable. In prostate cancer patients receiving androgen deprivation therapy, zoledronic acid given every 3 months resulted in an increase in BMD of 5.6% after 1 year compared with a decrease of 2.2% over the same time period in patients not given zoledronic acid, an overall difference of 7.8% (P < 0.001; ref. 17).
In postmenopausal osteoporosis, exposure to high i.v. doses of alendronate over 4 days induced a 5% increase in BMD at 1 year and had a sustained effect on bone resorption for at least 1 year (18, 19), whereas monthly oral ibandronate resulted in 6.6% and 4.2% increases in BMD after 2 years at the spine and hip, respectively (20). Reid et al. (9) showed that a single i.v. infusion of zoledronic acid produced mean increases in BMD 1 year later of 4.6% and 3.3% at lumbar spine and hip, respectively, and that this was as effective as more frequent dosing. In this latter study, the bone resorption marker urinary N-telopeptide/creatinine ratio [N-telopeptide of type II collagen (NTX)] decreased rapidly following zoledronic acid and remained suppressed after 1 year. Very recently, preliminary results of a large phase III trial of an annual schedule of 5 mg zoledronic acid indicated that this schedule was able to reduce the risk of osteoporotic fractures in spine, hip, and other nonvertebral sites (21).

These studies have raised the possibility that a single dose of a potent bisphosphonate in patients with low BMD may lead to a long-term decrease in bone resorption with increases in BMD beyond 1 year. In this exploratory open study, we report, for the first time, the long-term effects (up to 3 years) of a single i.v. infusion of zoledronic acid on BMD in long-term survivors from cancer with osteopenia.

**Patients and Methods**

Sixty-six cancer survivors with osteopenia, based on double-beam X-ray absorptiometry scan WHO T-score criteria (-1 SD to -2.5 SD from the sex-matched young adult mean, WHO Technical Report 1994), were recruited to a single-arm, open, phase II single center study. For this study, all patients in our center who were eligible (see below) and who were osteopenic on double-beam X-ray absorptiometry scanning were invited to participate. Recruitment commenced in October 2001 and was completed in December 2004. Only patients at least 1 year after a complete response of cancer to surgery ± chemotherapy and/or radiotherapy with no evidence of metastases were included. Other entry criteria included confirmation of postmenopausal status (females), Eastern Cooperative Oncology Group performance status ≤2, no previous bisphosphonate treatment, no treatment with anabolic steroids, fluoride, or calcitonin or change in endocrine therapy within the last 6 months, and absence of abnormal renal function and of other disorders of bone metabolism. For female patients, postmenopausal status was not only documented primarily by lack of menstruation for >1 year but was also assessed biochemically by using a combination of serum follicle-stimulating hormone ≥15 mIU/ml and estradiol levels within the postmenopausal reference range (see below). All patients who completed the main 2-year study were invited to participate in the extension study, which involved a further BMD and NTX assessment at 36 months. All patients gave written informed consent and the study was approved by the local Ethics Committee. On meeting the entry criteria, patients were given a single 15-min i.v. infusion of 4 mg zoledronic acid. All patients were prescribed daily oral calcium (500 mg) and vitamin D (400 IU).

BMD was measured at the lumbar spine (L1-L4) and nondominant hip using a Lunar Expert DXA Scanner (GE Lunar; ref. 22). The precision using the EXPERT-XL is 0.01 to 0.03 g/cm², depending on the site measured, with precision for the spine being greater than that for the proximal femur. Daily quality assurance was done whenever a patient was to be scanned, using a phantom, following the manufacturer’s guidelines. Measurements were made at baseline and then at 6, 12, 18, 24, and 36 months following zoledronic acid infusion.

NTX was measured at weeks 6 and 12, and 3 months thereafter until 24 months and then at 36 months on a second voided morning urine sample. These measurements were made by a chemiluminescence assay using a Vitros ECI analyzer (23) and urinary creatinine was measured using a dry slide method, in both cases using reagents from Ortho-Clinical Diagnostics (Rochester, NY). The NTX reference ranges used in our center were 16 to 107 nmol/mmol creatinine for males and 32 to 124 nmol/mmol creatinine for postmenopausal females (coefficient of variation, 6.8-14.9%). Testosterone was determined using the Vitros assay (reference range, 7.1-24.1 nmol/L). Estradiol was measured by the Elecsys assay systems (reference range, 5-54.7 pg/ml for postmenopausal females; Elecsys 2010 immunonanalyzer, Roche Diagnostics GmbH).

Blood samples were taken for safety measurements, including full blood count (hemoglobin, total white cell, neutrophil, and platelet count), urea and electrolytes, liver function tests, alkaline phosphatase, calcium and adjusted calcium, and inorganic phosphate, and any adverse events were recorded at each clinical visit. Spinal X-rays were not routinely carried out and only symptomatic fractures were recorded.

Changes in urine NTX and BMD were examined using a mixed model linear regression and analysis of covariance using SPSS for Windows (version 11.5.0). The analysis allows for missing values. Data from patients who withdrew from the study were included in the analyses up to the time of withdrawal. Significance of changes between baseline and individual time points were assessed by paired t tests. Where data were not normally distributed, statistics were conducted on log-transformed data. Figures of percentage changes from baseline are shown as means (SE).

**Results**

Forty-five females and 21 males were recruited (44 breast cancer, 11 testicular cancer, and 11 lymphoma). The mean ages

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**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Overall population</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>66</td>
<td>45</td>
<td>21</td>
</tr>
<tr>
<td>Mean time since last cancer therapy (range), y</td>
<td>50 (21-78)</td>
<td>54 (32-78)</td>
<td>42 (21-78)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>44</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>11</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Testicular</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Mean estradiol (range), pg/ml</td>
<td>N/A</td>
<td>15.3 (0.5-27.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean testosterone (range), nmol/L</td>
<td>N/A</td>
<td>N/A</td>
<td>11.5 (4.1-23.7)</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not applicable.
and mean times since last cancer treatment (with ranges) are shown in Table 1, along with gonadal hormone levels at baseline. Eighteen patients (all breast cancer) had received concomitant endocrine treatment. Of these, 13 had received tamoxifen alone (8 had completed tamoxifen before the study and the remaining 5 had been on tamoxifen for more than 2 years) and 5 had received tamoxifen and then an aromatase inhibitor. Two of these patients had completed aromatase inhibitor (anastrazole) treatment before study entry and three patients continued throughout the study. Using the lower limit of the reference range of testosterone (7.1 nmol/L), 3 of the 21 men were hypogonadal at baseline. Two of these were more elderly men with lymphoma and one was a younger man who had had testicular cancer.

Ten patients did not complete the 2-year main study with four withdrawing in the first 6 months and a further three by 12 months. In 2 patients, withdrawal was due to disease recurrence (1 lymphoma and 1 breast) and 8 due to patient logistical reasons (3 lymphoma, 3 testicular, and 2 breast).

Figure 1 shows the mean percentage change in BMD at the spine and hip, relative to baseline, at various times. For the spine, there was a mean increase in BMD at 12 months of 3.1% (range, -9.0% to 11.1%). By 24 months, a mean increase in BMD of 5.2% (range, -5.8% to 15.4%) was achieved and this was sustained at 3 years, with a mean increase of 5.3% (range, -1.5% to 15.8%). At all time points, the increases relative to baseline were highly significant ($P < 0.001$). At the hip, the BMD also increased steadily by 2.7%, 3.5%, and 4.3% (ranges, -4.6% to 11.0%, -3.5% to 12.0%, and -2.9% to 12.1%) after 12, 24, and 36 months, respectively ($P < 0.001$ at all time points).

The distribution of the change in BMD with time is shown in Fig. 2 in terms of the proportions of patients who suffered a loss in BMD, up to 3% increase in BMD and >3% increase in BMD, following the single infusion of zoledronic acid. The majority of patients already showed an increase in BMD by 6 months and this proportion increased with time on study and three patients continued throughout the study. Using the lower limit of the reference range of testosterone (7.1 nmol/L), 3 of the 21 men were hypogonadal at baseline. Two of these were more elderly men with lymphoma and one was a younger man who had had testicular cancer.

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The distribution of the change in BMD with time is shown in Fig. 2 in terms of the proportions of patients who suffered a loss in BMD, up to 3% increase in BMD and >3% increase in BMD, following the single infusion of zoledronic acid. The majority of patients already showed an increase in BMD by 6 months and this proportion increased with time on study (76%, 85%, and 84% at the spine and 87%, 85%, and 90% at the hip, recorded at 12, 24, and 36 months, respectively). The numbers of patients gaining BMD were higher at the hip than at the spine but Fig. 2 shows that the rate of gain and the magnitude of the gain were greater at the spine than at the hip. At the spine, only 3.8% patients lost >3% in BMD (maximum individual loss, 5.8%) over 24 months, although 1 patient lost 9% at 3 years. At the hip, only one patient (1.9%) lost >3% in BMD (actual value, 3.5%) at 24 months.

Figure 3 shows an early and substantial mean percentage decrease in NTX of ~60% at 6 weeks. This reduction was substantially maintained for the rest of the study period, with around a 40% reduction at 12 months and a 32% reduction maintained at 24 months. Even at 3 years, the reduction remained at ~30% ($P < 0.001$ at all time points).

Because the study population contained a mix of men and women, we have analyzed the BMD changes overall and by gender. These analyses are reported in Table 2 for 12, 24, and 36 months. For both men and women, the differences between BMD values at all time points and those at baseline were highly significant ($P < 0.001$). Moreover, statistical analysis showed that there was no significant sex-time interaction for spine ($P = 0.285$) or for hip ($P = 0.629$). Corresponding analyses for the NTX changes in men and women are also shown in
Table 2, including 6 weeks (by which time the maximum change had occurred) and 6, 12, 24, and 36 months. Again, for both men and women, at all time points, the differences compared with baseline were highly significant ($P < 0.001$). Further statistical analysis showed that there was no significant sex-time interaction ($P = 0.637$). These data therefore show that there is no significant difference in BMD and NTX change between men and women in the response to zoledronic acid.

There were no serious drug-related adverse events, including renal toxicity or reported osteonecrosis of the jaw. No patient required hospital admission due to drug toxicity. Reported drug toxicities included flu-like symptoms (63%), nausea (6%), headache, bone ache, and itching (each <5%). One patient suffered a low trauma Colles wrist fracture while on study.

**Discussion**

This is the first demonstration of a sustained increase in BMD over several years from a single dose of a bisphosphonate in patients with cancer treatment–induced bone loss or, indeed, in any condition resulting in low BMD. The results in the current study are consistent with the shorter study by Reid et al. (9), which reported similar increases at the spine and at the hip 1 year after an infusion of 4 mg zoledronic acid in postmenopausal women with low BMD, but provide additional information on the duration of action of a single treatment. Correspondingly, in 40 men with prostate cancer receiving a GnRH agonist, Michaelson et al. (24) have shown very recently that a single treatment with zoledronic acid significantly increased BMD relative to placebo 1 year later (spine, 4.0% increase compared with a loss of 3.1% in placebo, $P < 0.001$; hip, 0.7% increase compared with 1.9% loss in placebo, $P = 0.004$).

We believe that our data represent the longest-lasting effect of a single dose of a bisphosphonate yet reported. It is noteworthy that BMD continued to increase after 1 year, and it was not simply that the early increase was sustained with 85% patients achieving an increase at spine and 90% at the hip after 3 years. Because the study population was of mixed gender, it was important to determine if there was any sex-linked dependence of the response to zoledronic acid. Our results show clearly that there was no such dependence. Although tamoxifen therapy itself is known to have a slight beneficial effect on BMD in postmenopausal women, recent studies have shown that most of this gain occurs within the first 2 years of therapy (25). In the current study, 18 women had received tamoxifen therapy, all for at least 2 years, and the majority had completed tamoxifen before study entry.

The large reduction in urinary NTX levels after 6 weeks (~60%) is consistent with other studies following infusion of 4 mg zoledronic acid (26) but, remarkably, the mean NTX suppression below baseline was still 30%, even 3 years after

<table>
<thead>
<tr>
<th>Time after zoledronic acid (mo)</th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPINE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3.09 ± 0.55 (59)</td>
<td>3.05 ± 0.7 (42)</td>
<td>3.21 ± 0.87 (17)</td>
</tr>
<tr>
<td>24</td>
<td>5.18 ± 0.68 (53)</td>
<td>4.99 ± 0.84 (40)</td>
<td>5.75 ± 1.06 (13)</td>
</tr>
<tr>
<td>36</td>
<td>5.26 ± 0.89 (38)</td>
<td>5.45 ± 1.19 (27)</td>
<td>4.81 ± 1.03 (11)</td>
</tr>
<tr>
<td><strong>HIP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2.67 ± 0.41 (59)</td>
<td>2.97 ± 0.52 (42)</td>
<td>1.93 ± 0.60 (17)</td>
</tr>
<tr>
<td>24</td>
<td>3.52 ± 0.46 (53)</td>
<td>3.69 ± 0.57 (40)</td>
<td>3.00 ± 0.69 (13)</td>
</tr>
<tr>
<td>36</td>
<td>4.27 ± 0.65 (38)</td>
<td>4.27 ± 0.84 (27)</td>
<td>4.28 ± 0.91 (11)</td>
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<tr>
<td><strong>NTX</strong></td>
<td></td>
<td></td>
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<tr>
<td>1.5</td>
<td>58.0 ± 3.2 (53)</td>
<td>58.5 ± 4.0 (39)</td>
<td>56.5 ± 5.3 (14)</td>
</tr>
<tr>
<td>6</td>
<td>45.7 ± 3.3 (51)</td>
<td>46.3 ± 4.2 (37)</td>
<td>44.1 ± 4.9 (14)</td>
</tr>
<tr>
<td>12</td>
<td>42.2 ± 3.9 (52)</td>
<td>42.8 ± 4.9 (36)</td>
<td>40.6 ± 6.22 (16)</td>
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<tr>
<td>24</td>
<td>32.6 ± 4.1 (41)</td>
<td>34.6 ± 5.12 (27)</td>
<td>28.8 ± 7.2 (14)</td>
</tr>
<tr>
<td>36</td>
<td>31.4 ± 6.4 (33)</td>
<td>28.6 ± 8.58 (23)</td>
<td>37.9 ± 7.4 (10)</td>
</tr>
</tbody>
</table>
treatment. Based on known correlations between BMD, reduction in bone resorption as reflected by NTX, and fracture rate (27–29), it seems likely that infrequent zoledronic acid administration would translate into clinical benefit, with reduced skeletal morbidity.

No placebo group was used in this study. We have justified this based on data from the study by Fleisch (3), where no increase in BMD was observed in the placebo group and also because, because it is the norm for a gradual reduction in BMD with age, particularly in the early postmenopausal years, the benefits of zoledronic acid over no treatment are more likely to be underestimated rather than overestimated in our study. Although there is some evidence that calcium and vitamin D supplementation may lead to a small reduction in bone markers of ~10% (9, 30), there is no convincing evidence that this alone can lead to an increase in BMD.

Recently, Black et al. (31) reported data from a double blind trial in which 1,099 postmenopausal women were randomized to receive either alendronate weekly for 10 years or alendronate weekly for 5 years followed by 5 years on placebo. Compared with continuing alendronate, switching to placebo for 5 years resulted in declines of BMD at the hip and spine of -2.4% (P < 0.001) and -3.7% (P < 0.001), respectively, but mean levels remained at or above the pretreatment levels 10 years earlier. This work has raised the possibility of providing a ‘drug holiday’ for those patients who are on long-term bisphosphonates. Such studies also serve to show the potential lasting effects of bisphosphonate therapy.

The duration of effect of a single dose of zoledronic acid found in the current study is unexpectedly long and a full biological explanation will require further studies. However, it is known that the duration of action of individual bisphosphonates varies according to their binding affinity to bone. This is extremely high for zoledronic acid compared with, for example, resoridronate (32). Following the acute effects of a bisphosphonate on local osteoclast function, the drug is presumably internalized by deposition of new bone but becomes biologically active again as this area undergoes subsequent remodeling months or years later. The high affinity of zoledronic acid for bone may result in the majority of this remobilized drug readhering to the bone surface and the consequent effects on bone cell function.

Although this study was done in a patient population with a history of cancer, it seems likely that our findings would apply also to accelerated bone loss from other causes, including postmenopausal osteoporosis. The findings have opened up the intriguing possibility of very infrequent use of a bisphosphonate to prevent accelerated bone loss, perhaps once every 2 to 3 years. This may be especially applicable in those patients with a milder degree of bone loss, with all the advantages that would accrue in terms of convenience, reduced toxicity, improved compliance, and cost.

References

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