Assessment of renal toxicity and osteonecrosis of the jaws in patients receiving zoledronic acid for bone metastasis

D. Aguiar Bujanda*, U. Bohn Sarmiento, M. Á. Cabrera Suárez & J. Aguiar Morales
Servicio de Oncología Médica, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain

Received 16 June 2006; revised 21 September 2006; accepted 25 September 2006

Background: Bisphosphonates (BP) decrease the incidence of skeletal related events among cancer patients with bone metastases from solid tumors and multiple myeloma. Renal safety and osteonecrosis of the jaws (ONJ) are two major concerns of toxicity. Information about safety of using BP beyond 2 years is scarce.

Materials and methods: Patients receiving zoledronic acid (ZA) at the time of the study were reviewed. Serum creatinine levels (SCL) were collected at three different moments: before the start of BP (baseline), at the time of analysis (final), and the highest SCL during the treatment (highest). Oral examination was carried out in every patient. Separated analysis was made for patients on BP for >2 years. Concomitant risk factors for both renal toxicity and ONJ were evaluated.

Results: Sixty-seven patients were included. Median time of BP was 22 months, with 22 patients receiving BP for >2 years. Median baseline and final values of SCL were 0.71 mg/dl and 0.70 mg/dl, respectively (P = 0.121). Median highest SCL during treatment was 0.82 mg/dl (P <0.0001). A notable increase in the SCL was observed in six of the 67 patients (9%), four of them receiving BP for >2 years (P = 0.085). ONJ was also diagnosed in six patients, four of them in the group of prolonged BP treatment.

Conclusion: ZA showed to be safe with a low rate of reversible renal toxicity. Patients receiving BP should be monitored carefully for renal toxicity and ONJ, especially those with exposure to BP beyond 2 years.

Key words: bisphosphonates, bone metastasis, osteonecrosis of the jaws, renal toxicity, zoledronic acid

introduction

Intravenous (i.v.) bisphosphonates (BP) are potent inhibitors of osteoclast-mediated bone resorption and decrease bone turnover. BP therapy has shown to reduce the incidence of skeletal related events (SRE) in patients with multiple myeloma (MM) and bone metastasis from solid tumors [1]. BP are well tolerated, with mild-to-moderate influenza-like symptoms following the initial infusions. Several complications such as electrolyte abnormalities (calcium, magnesium, and phosphorus), acute systemic inflammatory reactions, ocular complications, and nephrotic syndrome occur in <2% of patients participating in clinical trials [2]. Renal toxicity and osteonecrosis of the jaws (ONJ) have, however, emerged as a major concern of BP therapy in the last few years. Renal toxicity is rare when BP are administered at the recommended doses and schedules; nevertheless, renal function monitoring is advised during treatment [3]. In large randomized BP trials, the renal safety of zoledronic acid (ZA) and pamidronate disodium (PD) was similar, and in the case of ZA it was comparable to placebo [4–8]. In 2003, however, a report of the US Food and Drug Administration about 72 patients with renal failure after ZA therapy raised the concern about patient’s safety [9]. Twenty-seven patients required dialysis and 18 died. This report, however, did not consider other concomitant factors of renal toxicity, and the estimated incidence of this complication was <0.02% among >430 000 patients. The product label of PD and ZA was updated to include additional warnings of nephrotoxicity and restrictions for patients with varying degrees of renal impairment [10, 11]. In addition, information about renal safety of BP is scarce for treatments >2 years [12, 13].

Bisphosphonate-associated osteonecrosis of the jaws (BONJ) is also a rare complication, usually seen in patients receiving long-term therapy for BP [2, 14]. Since the first publication in 2003 about ONJ in patients receiving BP [15], several cases have been reported and ONJ was included in the product label of ZA. For these reasons we decided to investigate the incidence and risk factors of renal toxicity and BONJ in all our patients receiving ZA for bone metastasis, with special attention at those patients under treatment of >2 years.

materials and methods

From January to April 2006, all patients currently receiving BP were reviewed, resulting in 75 patients. Patients were included in the study
provided they had a diagnosis of bone metastasis from solid tumor or MM, and were receiving ZA at the time of the analysis. All patients received a 4-mg ZA infusion given for 15 min, every 3 or 4 weeks, and oral calcium plus vitamin D supplementation. Medical files of all patients were reviewed, and data about past medical history, concomitant therapy, and previous dental procedures were recovered. In addition, all laboratory exams were reviewed, and serum creatinine levels (SCL) were collected at the time of start of BP therapy (baseline), at the time of the analysis (final), and the highest SCL during the period of treatment (highest). Criteria for evaluating deterioration of renal function were adopted from previous studies [4–8, 13]. A notable SCL increase was defined as follows: an increase >0.5 mg/dl for patients with baseline SCL <1.4 mg/dl; an increase >1 mg/dl for patients with baseline SCL >1.4 mg/dl; or doubling over baseline. Renal toxicity (SCL increase) was also graduated according to the National Cancer Institute—Common Toxicity Criteria, version 3.0 (NCI-CTC, v3.0): grade 1, SCL greater than the upper limit of normal (ULN)—1.5 × ULN; grade 2, SCL >1.5–3.0 × ULN; grade 3, SCL >3.0–6.0 × ULN; grade 4, SCL >6.0 × ULN. A clinical oral examination was carried out monthly by the responsible oncologist of every patient during the study. Criteria for diagnosis of ONJ included an exposed necrotic bone in the mandible or maxilla (associated or not associated with pain, soft-tissue swelling, or purulent discharge) and a nonhealing necrotic bone or extraction socket (not necessarily after a dental procedure). Patients with suspected BONJ were sent for consultation and evaluated by a maxillofacial surgeon, who established the diagnosis and the appropriate management in every case. Statistical comparisons of differences between baseline versus final mean SCL were carried out using the paired-samples t test, and the Wilcoxon signed rank test was used for comparisons between highest SCL versus baseline and final SCL. The Fisher’s exact test was used to compare difference in proportions of BONJ and notable SCL increase among patients receiving BP for >2 years versus <2 years. Differences were considered statistically significant when P < 0.05; all P values were two-tailed. A logistic regression model was built to predict both renal toxicity and BONJ using the following risk factors: gender (male versus female), age (>65 years versus ≤65 years), use of steroids, use of nonsteroidal anti-inflammatory drugs (NSAID), arterial hypertension, diabetes mellitus, treatment with concomitant chemotherapy, treatment with concomitant biologic agents, and time on BP (52 years versus >2 years). The model was estimated using forward and backward selection (entry into the model if P < 0.05, removal from the model if P > 0.1). Statistical analysis was carried out using the SPSS software program (version 13.0; SPSS Inc., Chicago, IL).

**Results**

After an initial evaluation of 75 patients, 67 patients with full information of all variables were included in the study. Main characteristics for all patients and for patients with duration of treatment longer and shorter than 2 years are listed in Table 1. Median age at the time of study was 62 years (range 32–84 years), with 29 patients (43%) older than 65 years. Sixty patients (90%) were receiving concomitant antinecrosis therapy at the time of the study: 24 patients (36%) chemotherapy, 37 patients (55%) hormonal therapy (for breast and prostate cancer), and 10 patients (15%) biologic agents (six trastuzumab, two erlotinib, one thalidomide, and one bevacizumab). Other concomitant treatments included steroids in 15 patients and NSAID in 18 patients.

Median time on BP was 22 months (range 2–79 months). Ten patients had received PD previous to the initiation of ZA for a median time of 18 months (range 4–38 months).

### Table 1. Baseline characteristics of the patients [number (%)]

<table>
<thead>
<tr>
<th>Age</th>
<th>All patients (n = 67)</th>
<th>Treatment &lt;2 years (n = 45)</th>
<th>Treatment &gt;2 years (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>62</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>Range</td>
<td>32–84</td>
<td>32–84</td>
<td>37–83</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (34%)</td>
<td>18 (40%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Female</td>
<td>44 (66%)</td>
<td>27 (60%)</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>Primary cancera</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>35 (52%)</td>
<td>20 (44%)</td>
<td>15 (68%)</td>
</tr>
<tr>
<td>Lung</td>
<td>11 (16%)</td>
<td>10 (22%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>9 (13%)</td>
<td>7 (16%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>4 (6%)</td>
<td>4 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3 (4%)</td>
<td>2 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3 (4%)</td>
<td>1 (2%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Otherb</td>
<td>5 (7%)</td>
<td>4 (9%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Concomitant therapyc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>24 (36%)</td>
<td>20 (44%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>37 (55%)</td>
<td>22 (49%)</td>
<td>15 (68%)</td>
</tr>
<tr>
<td>Biologic agents</td>
<td>10 (15%)</td>
<td>5 (11%)</td>
<td>5 (23%)</td>
</tr>
</tbody>
</table>

aThree patients with double synchronic neoplasia, prostate cancer plus: lymphoma, multiple myeloma, and bladder cancer.

bTwo bladder cancer, one rectal cancer, one renal cancer, and one head and neck cancer.

cPatients could have been receiving one or more forms of therapy.

Median time on ZA was 20 months (range 2–52 months). Duration of BP >2 years was seen in 22 patients (33%).

### Renal Toxicity

Renal safety was assessed in all the 67 patients. Median baseline SCL in the whole group was 0.71 mg/dl (range 0.43–1.80 mg/dl), whereas median final SCL was 0.70 mg/dl (range 0.38–2.2 mg/dl) (P = 0.121). The median highest SCL during time of treatment was 0.82 mg/dl (range 0.52–2.2 mg/dl). Differences were significant between both the baseline and highest SCL (P < 0.0001) and the final and highest SCL (P < 0.0001). A notable increase in the SCL was observed in six of the 67 patients (9%), all of them females. Renal toxicity was observed in 14 patients (21%); grade 1 in four patients (6%, two males and two females), and grade 2 in 10 patients (15%, two males and eight females). No grade 3 or 4 renal toxicity was observed.

For the 22 patients receiving BP for >2 years, the median baseline SCL was 0.77 mg/dl (range 0.51–0.97 mg/dl) and the median final SCL was 0.74 mg/dl (range 0.47–2.2 mg/dl) (P = 0.097). The median highest SCL in this group was 0.90 mg/dl (range 0.58–2.2 mg/dl). A significant difference was detected between both the baseline and highest SCL (P < 0.0001) and the final and highest SCL (P < 0.0001). A notable increase in the SCL was observed in four of the 22 patients (18%) in this group, comparing with two of the 45 patients (4%) in the group of treatment <2 years. This difference did not reach statistical significance (P = 0.085). Renal toxicity was observed in six patients (27%); grade 1 in three patients (14%, one male and two females) and grade 2 in three patients (14%, three females).

**Table 1. Baseline characteristics of the patients [number (%)]**
In the logistic regression model, only the presence of diabetes mellitus was an independent factor for renal toxicity [odds ratio (OR) 6.806, 95% confidence interval (CI) 1.527–30.337; \( P = 0.012 \)].

Figure 1 displays median SCL at baseline, highest level, and at the moment of the study (final) for all the patients and for patients on BP for >2 years, respectively.

Most of the elevations of SCL were reversible and transitory, and only four patients (6%) had to stop treatment because of renal toxicity, and none of them needed dialysis.

**osteonecrosis of the jaws**

BONJ was diagnosed in six patients (9%). Characteristics of these patients are shown in Table 2. Mean age was 58 years (range 46–70 years), and five of them were females. Previous dental extraction was present in three patients (two of them have been previously reported elsewhere [16]), whereas three patients (50%) developed spontaneous ONJ. One patient was asymptomatic at the time of diagnosis of BONJ, which had been detected in routine oral examination. A total of nine lesions of BONJ were observed in six patients. Four patients had a single lesion, whereas two patients had more than one lesion of ONJ (two and three lesions). Location of the ONJ was exclusively in the posterior mandible in one patient, exclusively in the maxilla in three patients, and in both jawbones in two patients. After evaluation by a maxillofacial surgeon, all patients were managed with a conservative approach including antibiotic therapy and 0.12% chlorhexidine mouth rinse. In one patient, rounding off a sharp bone edge was necessary. ZA was discontinued in three patients (4%) because of extensive BONJ or progressive osteonecrosis. Patients with BONJ had a mean time on BP therapy of 34 months (range 10–58 months). In the group of patients receiving BP for >2 years the incidence of BONJ was 18% (four of 22 patients), compared with 4% for patients with treatment <2 years (two of 45 patients). This difference, however, was not statistically significant (\( P = 0.085 \)).

In the logistic regression model, only the presence of concomitant chemotherapy was an independent factor for BONJ (OR 29.117, 95% CI 1.488–569.798; \( P = 0.026 \)). Two of the six patients have died so far because of the underlying cancer and the remaining four patients have a stable or slowly improving BONJ.

**discussion**

The American Society of Clinical Oncology guidelines recommend continuation of BP therapy for bone metastasis until the patients' performance status deteriorates, despite the occurrence of SRE [17]. At the present time and with the newer treatments, it is not rare to obtain prolonged survivals in patients with bone metastases, especially in those with breast or prostate cancer. For this reason, it has become a frequent situation in the oncology practice to see patients who are receiving BP therapy for longer time.

It is well known that patients receiving BP therapy have a risk of an increase in their SCL, although in general it is clinically not significant and NCI-CTC grade 3 or 4 rarely occurs. Three large randomized trials of BP have investigated the long-term use of ZA and PD up to 2 years (21–24 months) in >3000 cancer patients with MM, lung cancer, breast cancer, and other solid tumors [4–8]. In a randomized, placebo-controlled trial of ZA in patients with skeletal metastases from lung cancer and other solid tumors [7, 8], there was a moderate, nonsignificant risk of increased SCL for the 4-mg ZA group compared with the placebo group (\( P = 0.228 \)). At the recommended 15-min infusion, the percentage of patients with increased SCL was 10.9% for the 4-mg ZA group versus 6.7% for the placebo group. The rate of grade 3 or 4 SCL increase was 1.8% for both the placebo and the 4-mg ZA groups. In another randomized, placebo-controlled trial of ZA in patients with hormone-refractory metastatic prostate carcinoma [6], the rates of renal function deterioration were 15.2% and 11.5% for the groups of 4-mg ZA and placebo, respectively. Grade 3 SCL increase rates were 3.3% and 1% for the 4-mg ZA and placebo groups, respectively. In these two studies of ZA versus placebo, the dose of 4 mg was considered less toxic than the dose of 8 mg, and the optimal infusion time was 15 min. A randomized trial
Table 2. Clinical characteristics of patients with ONJ (n = 6)

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60</td>
<td>67</td>
<td>46</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Primary cancer</td>
<td>Breast</td>
<td>Breast</td>
<td>Breast</td>
<td>Breast</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Concomitant anticancer therapy</td>
<td>Fulvestrant</td>
<td>Anastrozole</td>
<td>Letrozole</td>
<td>Paclitaxel</td>
<td>None</td>
</tr>
<tr>
<td>Time on BP (in months)</td>
<td>35</td>
<td>33</td>
<td>49</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>Symptoms of ONJ</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number of lesions of ONJ</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Location of ONJ</td>
<td>Left maxilla</td>
<td>Right maxilla</td>
<td>Left maxilla</td>
<td>Bilateral mandible</td>
<td>Right mandible and bilateral maxilla</td>
</tr>
<tr>
<td>Previous tooth extraction</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Both cases previously reported (see [16]).

Previous treatment with paclitaxel and gemcitabine.

Previous treatment with paclitaxel and trastuzumab.

F, female; M, male; BP, bisphosphonates; ONJ, osteonecrosis of the jaws.

of ZA versus PD in patients with breast cancer or MM [4, 5] showed a comparable risk of decreased renal function for ZA and PD after 2 years of therapy. A notable creatinine level increase was similar in both groups, 9.4% for ZA versus 6.5% for PD, with no case of NCI-CTC grade 3 or 4 SCL increase.

The result of these studies shows rates of notable increase of SCL very similar to those shown in our study (9%), although we had no case of grade 3 or 4 SCL increase.

Although experience with ZA and PD in general is extensive, information about renal safety of therapy beyond 2 years is scarce. In a retrospective review, 22 patients with breast cancer or MM receiving BP therapy for 2 years (mean 3.6 years, range 2.2–6.0 years) were reported [12]. The authors did not find any significant difference between mean creatinine level both at the entry of the study and at the time of the last value (0.9 and 1.1 mg/dl, respectively, \( P = 0.1 \)). In this study, however, there was neither a detailed analysis of NCI-CTC renal toxicity nor a description of notable SCL increase as reported in the previous studies referred above. In a second study comprising 57 patients treated with BP for >2 years (mean 34 months, range >24 to >131 months) [13], the criteria used for defining renal function deterioration were the same as that used in our study. A notable SCL increase was observed in seven patients (12.2%), and all were of NCI-CTC grade 1. In the 22 patients on ZA for >2 years analyzed in our study, we had a rate of 18% of notable SCL increase, with a rate of NCI-CTC grade 1 or 2 SCL increase of 27%. We observed that the rate of notable SCL increase was 18% for the group of treatment >2 years, compared with 4% for the group of shorter treatment, although this difference did not reach a statistical significance. The rates of NCI-CTC SCL increase, however, were similar for both groups of patients. As mentioned above, our data show that BP produces significant elevations in the SCL during therapy, although these elevations used to be reversible, since the differences on median SCL at baseline and at the final analysis are not statistically different.

The second safety point of our study was BONJ. This complication was described by 2003 [15], when thousands of patients had participated in clinical trials with no report of ONJ up to that date. This, in part, could be explained by the fact that most of the cases of ONJ have been described in patients with prolonged BP exposure. In the larger series of BONJ reported to date [14], the mean induction time for ONJ was 14.3 months for those who received PD, 12.1 months for those who received ZA and PD, and 9.4 months for those who received ZA.

More than 70% of the cases described are related to a previous dental extraction. In a study reporting 119 cases of BONJ [14], only 25.5% of the patients had no previous apparent dental disease, treatment, or trauma, whereas in another report [18], nine of the 63 patients (14%) had no recent history of dentoalveolar procedure. We have detected an unexpected high 50% rate of spontaneous BONJ (three of the six cases) although the number of patients in our study is too small.

The incidence of ONJ in patients receiving BP is difficult to estimate, because many cases come from isolated single case or retrospective case-series reports, and is thought to be between 2% and 9% of patients receiving i.v. BP. In a study of 252 patients receiving BP, there were 17 patients (6.7%) with BONJ [19]. Again, longer time on BP was a significant factor, resulting in an incidence of 1.5% among patients treated for <12 months and 7.7% for those treated for 37–48 months. A Web-based survey conducted by the International Myeloma Foundation reported a 6.2% incidence of ONJ among 1203 MM and breast cancer patients [20]. In another retrospective review on MM patients, a 3.2% incidence of BONJ was found, with 11 cases from a database of 340 patients [21]. A prospective study on MM patients treated with BP from 2003 assessed the development of ONJ in 202 patients and found an incidence of 7.4% (15 cases) [22]. Time of exposure to BP was significantly associated with the development of ONJ, with a cumulative hazard of 1% after 12 months of treatment rising to 15% at 4 years for patients treated with ZA. In our study, with the limitations of the small number of patients, there were six cases of BONJ, which represents 9% of the 67 patients analyzed. Due to the nature of our study, this 9% may better reflect the prevalence of BONJ more than a real incidence, since the six cases we report here are the only BONJ we have detected in our clinical practice, although we have the concern that some but rare cases (may be asymptomatic ones) could not be diagnosed in the past before the awareness of this new toxicity became noticed.
BONJ used to be painful, but up to 31% of cases can be asymptomatic and detected in routine oral examination [14]. Similar to other reports, one of the six cases was asymptomatic (detected in routine oral examination), and the mean time on BP before ONJ developed was large (mean 34 months, range 10–58 months). Our patients with BP therapy >2 years had a greater (although not statistically significant) risk of BONJ than those patients with treatment <2 years. The finding of patients with asymptomatic BONJ, and with more than one jaw lesion, supports the recommendation of routinely exploring the oral cavity of our patients receiving BP. An additional observation was that four of the six patients with BONJ had renal toxicity also. We have not found any relationship between these two toxic effects in previous studies, but one single explanation is that patients exposed for long time to BP have an increased risk of both BONJ and renal toxicity. Additional data from larger series are, however, needed to clarify this finding.

Studies of prognostic factors for renal toxicity and ONJ in patients under BP therapy are lacking. From our patient population we found that diabetes mellitus was an independent factor for renal toxicity, whereas concomitant chemotherapy was an independent factor for BONJ, with no significance for gender, age, time on BP, use of steroids, use of NSAID, concomitant chemotherapy or biologic agents, and arterial hypertension. Although not significant in our study, we found more cases of renal toxicity and BONJ in the group on BP treatment for >2 years, and we recommend special attention be given to those patients. Further studies addressing prognostic factors, however, are needed. Future retrospective analysis from larger series of patients could help us to better understand the real incidence and predisposing factors of BONJ, as well as to understand the mechanisms involved in this process.

Emerging evidence indicates that ibandronate, another BP available in both i.v. and oral presentation, has a more convenient renal toxicity profile than ZA or PD [23], although direct comparisons between these agents have not been published so far. Oral ibandronate can be an attractive alternative to ZA especially in patients not receiving additional i.v. therapy. Oral ibandronate, however, is not free of gastrointestinal toxicity and cannot be given to patients with severe renal impairment, and, with other oral medications, a major issue of concern is patient compliance with the dosing regimen.

**references**