Osteonecrosis of the jaw in patients with cancer who received zoledronic acid and bevacizumab

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Background. The authors investigated the incidence of and risk factors for osteonecrosis of the jaw (ONJ) in patients with metastases to the bone who received the bisphosphonate agent zoledronic acid (ZOL) and chemotherapy combined with the antiangiogenic agent bevacizumab (BEV).

Methods. The authors evaluated 59 participants (34 with breast cancer and 25 with nonsmall-cell lung cancer). All of the participants received 4 milligrams of ZOL via intravenous (IV) infusion every four weeks and 15 mg per kilogram of BEV every three weeks. They conducted a dental examination in participants at baseline and every three months until the patients died or were lost to follow-up. If needed, participants received periodontal disease treatment and underwent tooth extraction before they started receiving ZOL and BEV.

Results. The median time the participants received ZOL therapy was 18.8 months (range, 3.1-28.9 months); 36 participants (61.0 percent) received ZOL therapy for more than one year. The median time participants received BEV therapy was 16.7 months (range, 2.8-29.6 months). None of the participants required dentoalveolar surgery while undergoing cancer treatment. After a median follow-up period of 19.7 months, none of the participants developed bisphosphonate-related ONJ.

Conclusions and Clinical Implications. ZOL combined with BEV did not predispose to ONJ participants with cancer that had metastasized to the bone who underwent a baseline dental examination and preventive dental measures. The study results must be considered in the context of the study’s protocols and the follow-up period.

Key Words. Bevacizumab; bisphosphonates; bone markers; bone metastases; osteonecrosis of the jaw; zoledronic acid.

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during treatment seem to play a major role in the development of ONJ.\textsuperscript{7,9} A plausible mechanism for osteonecrosis related to BP therapy is an alteration in the normal bone homeostasis process that repairs physiological microdamage.\textsuperscript{10,31} A theory that BRONJ is a form of avascular necrosis similar to osteoradionecrosis has also been proposed.\textsuperscript{10,12} The results of an in vitro study have shown that ZOL exhibited antiangiogenic properties such as causing ischemic changes.\textsuperscript{13} These antiangiogenic effects, together with microtrauma, inflammation and chronic infections, might play a role in the development of ONJ. Therefore, BRONJ may be due to a complex interplay of suppressed bone remodeling and hypovascularity compounded by local mechanical or infectious trauma.\textsuperscript{14}

One of the antiangiogenic agents used in cancer treatment is bevacizumab (BEV). It is a humanized murine monoclonal antibody against vessel endothelial growth factor, which is administered in combination with chemotherapy for first-line treatment of patients with metastatic breast and nonsmall-cell lung (NSCL) cancer. The use of BEV has shown improvement in overall survival time (median time, about 25-30 months and 12-18 months in patients with breast and NSCL cancer, respectively).\textsuperscript{15} We hypothesize that the combination of this antiangiogenic agent with ZOL can lead to the enhancement of bone tissue avascularization, which can account for a potentially higher incidence of ONJ in patients with metastases to the bone who receive this type of treatment.\textsuperscript{16,17} We conducted a study to investigate the incidence and risk factors of ONJ in patients with metastases to the bone from solid tumors who were treated with ZOL and a multiagent regimen including BEV in our cancer center (Medical Oncology Division, University of Siena, Italy).

**PARTICIPANTS AND METHODS**

In our study, which was the secondary endpoint of a clinical study regarding the use of chemotherapy plus BEV therapy in patients with metastatic breast and NSCL cancer, we used a dental substudy protocol to assess ONJ.

The primary endpoint of our clinical study was to investigate the serum changes in bone markers in patients receiving a potentially high antiresorptive treatment, such as the combination of ZOL with the antiangiogenic agent BEV. Assuming that there is an approximately 60 percent decrease in the bone resorption marker C-terminal telopeptide (CTX) serum levels after three months of treatment with ZOL in patients with metastases to the bone, the original design of the study required the enrollment of at least 62 patients to detect a 15 percent difference in the median percentage change in CTX with the novel combination of ZOL and BEV (\(\beta = 0.20\) and \(\alpha = .05\)).\textsuperscript{18} Data regarding bone resorption markers will be presented in another article.

We included in our study patients 18 years or older, who had an Eastern Cooperative Oncology Group performance status of 2 or less\textsuperscript{19} and at least one site of metastases to the bone secondary to breast or NSCL cancer. We excluded patients if they had metastases to the liver with total bilirubin levels greater than 2.5 milligrams per deciliter, a serum creatinine level greater than 3.0 mg/dL or symptomatic metastases to the brain. We also excluded patients if they had been exposed to intravenous (IV) BP, had a severe cardiovascular disease, had hypertension refractory to treatment or had symptomatic coronary artery disease. The institutional review board at the University of Siena approved the study, and all participants provided written informed consent.

At baseline and at three and six months, we obtained venous blood samples from participants between 8 and 9 a.m. after they had fasted for 12 hours to assess the serum level of cross-linked CTX (s-CTX) (Serum Cross Laps ELISA, Nordic Bioscience Diagnostics, Herlev, Denmark). We performed a complete blood chemistry panel that included serum electrolytes, calcium and magnesium at baseline and then every three weeks.

For a maximum of two years, all of the participants received 4 mg of ZOL via a 15-minute IV infusion in 100 milliliters of saline solution every four weeks until the occurrence of severe adverse events.

We administered BEV intravenously to all participants at a dose of 15 mg per kilogram of body weight every three weeks. The first-line chemotherapy included a docetaxel injection, a paclitaxel injection or an epirubicin injection plus...
clomiphosphamide in participants with breast cancer, and cisplatin plus gemcitabine hydrochloride or cisplatin plus etoposide phosphate intravenously in participants with NSCL cancer.

Before we administered the first-line treatment to the participants, we conducted a complete physical examination, tumor assessment, bone scan and bone survey for each participant.

For each participant, we conducted a dental examination and obtained panoramic radiographs, at baseline, and we conducted a dental examination every three months until the patient died or was lost to follow-up. The measures we took to reduce participants’ risks of developing ONJ are shown in the box. The criteria we used to diagnose 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 subsequent to a dental procedure).

RESULTS

From July 2007 to December 2009, we enrolled 34 participants with metastases to the bone from breast cancer (57.6 percent) and 25 participants with metastases to the bone from NSCL cancer (42.4 percent) in our study investigating the activity of chemotherapy and BEV in solid tumors. We followed up all of the participants for a minimum of six months and included them in our analyses. The main baseline characteristics of all participants and of participants who received ZOL one time or less per year and more than one time per year are listed in Table 1. The median time the participants received ZOL therapy was 18.8 months (range, 3.1-28.9 months); 36 participants (61.0 percent) received ZOL therapy for more than one year. The median time participants received BEV was 16.7 months (range, 2.8-29.6 months).

After six months, three participants with breast cancer and seven participants with NSCL cancer required changes in the chemotherapy protocol and discontinuation of BEV owing to disease progression; ZOL therapy was continued in all of these participants. One participant with breast cancer was lost to follow-up after 13 months of treatment, and one participant with NSCL cancer was lost to follow-up after 16 months of treatment.

Of the 59 participants, 41 (69.5 percent) had a baseline s-CTX serum level above the normal range. The percentage of participants with changes in s-CTX serum level during treatment appeared similar to that usually reported with BP use and conventional treatments not including BEV (data not shown).

After a median follow-up period of 19.7 months, none of the participants developed ONJ. Table 2 (page 510) depicts putative dental risk factors for ONJ and associated comorbidities in our study population. We recommended maintenance of and improvement in oral hygiene home care routines for all participants, and we treated dental caries in 15 participants. Before participants with periodontal disease started receiving therapy, we treated infective foci with 875 mg of amoxicillin and 125 mg of clavulanic acid orally three times a day and provided mouthrinses with chlorhexidine and local antibiotic agents (for example, rifampin). After we conducted the baseline dental examinations and obtained the panoramic radiographs, we had to extract teeth in seven participants to prevent the need for dentoalveolar surgery. Considering time allowed for healing and the recommendations for the use of BEV after surgical procedures, these participants began receiving the combination of BEV and ZOL at least four weeks after tooth extraction. All of these participants received BEV for more than nine months and ZOL for more than 12 months. Six other participants had undergone tooth extraction during the 12 months before they began undergoing chemotherapy. Clinical photographs and radiographs of two participants are shown in Figures 1 and 2 (page 511).

One participant had rheumatoid arthritis, a comorbidity that may be associated with an increased risk of developing ONJ, and was receiving corticosteroid medication. Nine par-
TABLE 1

Baseline characteristics.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>ALL PARTICIPANTS</th>
<th>PARTICIPANTS RECEIVING ZOLEDRONIC ACID ONE TIME PER YEAR OR LESS</th>
<th>PARTICIPANTS RECEIVING ZOLEDRONIC ACID MORE THAN ONE TIME PER YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL (No.)</td>
<td>59</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Median Age (Years [Range])</td>
<td>64 (44-80)</td>
<td>63 (48-80)</td>
<td>65 (44-79)</td>
</tr>
<tr>
<td>No. of Bone Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>31</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>≤ 3</td>
<td>28</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>41</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Primary Cancer (No. of Patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>34</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Nonsmall-cell lung</td>
<td>25</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Serum Level of Cross-linked C-Terminal Telopeptide* (Nanograms Per Milliliter [Range])</td>
<td>1.29 (0.16-3.34)</td>
<td>1.04 (0.16-3.34)</td>
<td>1.31 (0.18-3.21)</td>
</tr>
<tr>
<td>First-Line Treatment (No. of Patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel injection plus BEV†</td>
<td>13</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Docetaxel injection plus BEV</td>
<td>17</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Docetaxel injection and epirubicin injection plus BEV</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cisplatin and gemcitabine hydrochloride plus BEV</td>
<td>19</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Cisplatin and etoposide phosphate intravenously plus BEV</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Received BEV for More Than Six Months (No. of Patients)</td>
<td>46</td>
<td>17</td>
<td>29</td>
</tr>
</tbody>
</table>

* Expressed as median values.
† BEV: Bevacizumab.

Participants who had osteoporosis had received the BP alendronate orally with calcium and vitamin D₃ supplementation between one and six years before starting treatment. Other comorbidities we observed were diabetes mellitus, osteoarthritis and osteoporosis.

While 13 participants who developed periodontal diseases and infective foci were undergoing cancer treatment, we successfully treated them by means of nonsurgical procedures, antibiotic agents and antimicrobial mouthrinse. None of the participants required dentoalveolar surgery while undergoing cancer treatment.

DISCUSSION

In our study, 59 participants with metastases to the bone from breast and NSCL cancer received ZOL and chemotherapy combined with the antiangiogenic agent BEV. After a median follow-up time of 19.7 months, we did not detect ONJ in any of the participants. These results are comparable with (or even more favorable than) those reported in most clinical trials regarding conventional cancer treatment.⁶-¹⁰ Therefore, despite the fact that new and potent antiangiogenic therapies theoretically might enhance the antiangiogenic effects of ZOL on bone tissue, our findings do not indicate a trend of a higher incidence of BRONJ in patients receiving ZOL and BEV.¹⁶,¹⁷ Nevertheless, evidence showing that antiangiogenesis is the main underlying mechanism of BRONJ still is lacking.

Although the small sample size in our study did not allow us to draw firm conclusions, this was, to our knowledge, the first prospective study of ONJ in patients exposed to ZOL and to the antiangiogenic agent BEV. The preventive dental measures taken at our cancer center before participants received therapy (Box) may have contributed to the fact that none of the participants developed BRONJ while participating in the study. Moreover, patients’ characteristics do not suggest that the putative risk
factors for ONJ are similar to and not better than those usually observed in patients with breast and NSCL cancer in terms of type and incidence. We did not, however, show that ONJ did not develop in participants who received ZOL and BEV because we did not perform any dental treatment in these participants while they were receiving the drugs. All of the treatment was preventive and performed before they received ZOL and BEV.

The median time of exposure to BP, which is associated substantially with the development of ONJ, was 18.8 months in our study, which may be considered sufficiently long, especially for patients with metastatic breast and NSCL cancer who usually have a poor prognosis. In a study of 252 patients receiving BP, investigators detected ONJ in 17 patients (6.7 percent), with an incidence of 1.5 percent among patients treated for less than 12 months and 7.7 percent for those treated for more than 12 months. The results of a study of 202 patients with multiple myeloma showed that ONJ developed in 7.4 percent of patients, with a cumulative hazard rate of 1 percent after 12 months of treatment that increased to 15 percent at four years for patients treated with ZOL. The results of a large BRONJ study with 119 participants showed that the mean induction time for ONJ was 14.3 months for patients who received pamidronate disodium, but it was only 9.3 months for those receiving ZOL. Therefore, since 61.0 percent of the participants in our study received ZOL for more than 12 months, most of the patients in our study must be considered at high risk of developing ONJ. Moreover, since 46 of the patients in our study received BEV at a dose of 15 mg/kg of body weight every three weeks for more than six months, they were at risk of developing ONJ. Although a longer follow-up period would have been useful in verifying the incidence of ONJ in our study, we were limited by the median survival rate of our study population.

Even with the limits of a retrospective analysis, the investigators of a study involving 4,019 patients who received BP intravenously identified dental extractions and periodontal
disease as precipitating factors in the development of ONJ in 55 percent and 41 percent of patients, respectively. In our study, after the baseline dental examination, seven participants needed to undergo tooth extraction, and we performed the extractions before the participants started taking ZOL and BEV. The participants avoided undergoing other dentoalveolar surgical procedures while they were receiving treatment, probably owing to the baseline preventive dental examination and the follow-up examinations. Therefore, the results of our study have shown that a dental examination can minimize the risk of developing ONJ but not that ZOL and BEV are not a cause of ONJ or that it is safe to provide dental care when patients are receiving ZOL and BEV therapy.

Among other potential risk factors, we found elevated baseline serum levels of the bone resorption marker CTX in most of the participants. However, these increased levels had no apparent association with an increased risk of developing ONJ. The measurement of biochemical markers of bone metabolism can provide
useful information about the effects of BP and underlying cancer therapy, but further research is needed to investigate the possible role of bone markers as biomarkers in patients with BRONJ.22,23

There are few reports concerning the incidence of ONJ in patients treated with the combined use of IV BPs and other antiangiogenic agents. In a retrospective study, 74 patients with cancer in an advanced stage received the antiangiogenic agents BEV, bortezomib and thalidomide.24 The study’s investigators found that there was a negative association between the use of these agents and ONJ development. On the other hand, investigators conducting another retrospective analysis found an ONJ incidence of 16 percent and 1.1 percent among patients with cancer who were receiving BPs with or without antiangiogenic agents (for example, BEV or sunitinib), respectively.25 The value of these findings is limited by the retrospective nature of the studies and the fact that baseline and follow-up dental examinations during treatment were not conducted.

The investigators in a recent phase II clinical trial enrolled 60 patients with metastatic castrate-resistant prostate cancer to receive BEV, docetaxel, thalidomide, prednisone and IV BPs (92 percent received ZOL).26 The results showed an 18.3 percent incidence of ONJ during the study (20 percent for patients receiving ZOL), which was higher than the usual incidence of BRONJ (1 to 10 percent). As the investigators pointed out, however, it was a retrospective analysis, and a baseline dental examination was not included in the clinical trial. Many other factors may play a role in the pathogenesis of BRONJ, and further research is needed to elucidate the complex interactions of BP with chemotherapy and with antiangiogenic therapies.27 However, in spite of not knowing the exact pathophysiological mechanism and the fact that an increased risk of developing ONJ after IV BP has been reported in retrospective studies,3-10 our results suggest that having patients undergo a baseline dental examination and appropriate dental procedures before starting BP therapy may reduce substantially the incidence of ONJ.

CONCLUSIONS

Although further research is needed, the results of our study suggest that ZOL combined with the antiangiogenic agent BEV does not predispose patients with metastases to the bone from breast and NSCL cancer to ONJ if they undergo a baseline dental examination. Nevertheless, the results of the study must be considered in the context of the follow-up period used in the study and the use of the preventive dental protocol.

We hope these results will help general dentists, oral surgeons and oncologists in their efforts to prevent BRONJ and identify at-risk patients by means of careful baseline and follow-up dental examinations while they receive cancer treatment.

Disclosure. None of the authors reported any disclosures.


