Dental extraction as a risk factor for bisphosphonate related osteonecrosis of the jaw in cancer patients: an update

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Abstract

Osteonecrosis of the jaw (ONJ) is a complication related to the use of bisphosphonates (BPs). Patients receiving BPs for the treatment of malignancies are at an increased risk of developing bisphosphonate-related ONJ (BRONJ) as compared to patients receiving BPs for the treatment of other disorders such as osteoporosis. Additionally, tooth extractions have been suggested to increase the risk of BRONJ in individuals taking BPs.

Objective: To review the role of dental extraction as a risk factor for BRONJ in cancer patients.

Materials and methods: Databases were searched from January 1999 up to and including July 2012 using various combinations of the following keywords: “bisphosphonate”, “osteonecrosis of the jaw”, “cancer”, “oral” and “dental extraction”.

Results: Twenty two studies were included. Eighteen studies assessed the relationship between BRONJ and dental extractions in cancer patients, reporting the overall prevalence of BRONJ following extraction in this group as 3.25 ± 2.23%. Four studies did not report a correlation between BRONJ and extractions, and recommended protocols to avoid the complication.

Conclusion: There is a plausible relationship between dental extractions and the development of BRONJ in cancer patients. Written informed consent must be obtained prior to dental procedures in patients at risk for developing BRONJ.

Keywords: Bisphosphonate, cancer, jaw, osteonecrosis, tooth extraction
Introduction

Bisphosphonates (BPs) were developed about 30 years ago as a class of drugs used for the treatment of bone diseases. These are analogs of a naturally occurring compound, pyrophosphate that serves to regulate calcium metabolism (1). Their primary mode of action is the regulation of bone turnover by inhibition of bone resorption. At the cellular level, BPs shorten the lifespan of osteoclasts and reinforce the proliferation of osteoblasts. This translates to an increased bone mineral density, maintenance or improvement of structural and material properties of bone, and reduced risk of fractures (2, 3).

BPs are classified as either nitrogen-containing or non-nitrogen containing BPs. Nitrogen-containing BPs alter the cytoskeleton of osteoclasts and block essential enzyme synthesis whereas non-nitrogenous bisphosphonates inhibit osteoclastic activity by a direct cytotoxic effect to induce apoptosis (4). Further, depending on the route of administration, BPs can be categorized as either oral or intravenous (IV) (5).

Despite the therapeutic benefits of BPs, these drugs have been implicated in causing osteonecrosis of the jaw (ONJ) (6). The MARX study (7) identified 36 cases with painful exposure of the bone in the maxilla and mandible of subjects receiving BPs. The prevalence of ONJ is reported to be higher with IV BPs as compared to oral BPs. CARTSOS et al. (8) studied a medical insurance claims database and found that IV BPs significantly increased the risk of inflammatory jaw conditions compared with oral BPs. This may be attributed to the fact that the oral cavity and associated structures are richly vascularized, which increases the concentration of bisphosphonates in this area (9).

However, even after numerable reports of bisphosphonate related ONJ (BRONJ) over the years, a consensus regarding the triggering factors for this condition has not emerged. BPs are also routinely prescribed to cancer patients for the management of primary or secondary malignancies affecting the skeleton (2).

The risk of BRONJ following BP therapy in these patients has not yet been definitively quantified. Prevalence rates as high as 1 to 5% have been reported, depending on related factors such as treatment duration (10). The most commonly reported inciting factor for the onset of symptoms is dento alveolar bone manipulation that occurs during tooth extraction. A recent study that surveyed subjects with pertinent dental symptoms revealed BRONJ prevalence to be 0.1% to 0.2% among survey respondents (11). On the other hand, a regional study by MAVROKOKKI et al. (12) estimated the prevalence associated with oral alendronate use to be 0.01 to 0.04% ; however, the risk of BRONJ increased dramatically, by as much as four times when they underwent a dental extraction.

Overall, data regarding the prevalence of BRONJ is inconclusive due to a dearth of indexed literature in this regard. The aim of this study was to review the role of dental extractions as risk factors for the prevalence of BRONJ in cancer patients.
Materials and methods

Focused question
Is there an established relationship between tooth extraction and the onset of BRONJ in cancer patients?

Eligibility criteria
The following eligibility criteria were imposed: Randomized controlled trials (RCTs), retrospective and prospective studies, and surveys from the literature published in English language. Studies were screened and specifically selected on the basis of the following levels of evidence:

- administration of BPs to treat metastatic cancers and documentation of BRONJ,
- total number of subjects/subject records examined,
- prevalence of BRONJ in the cancer subjects,
- number of cancer subjects that have undergone dental extractions.

Case reports, studies with less than 30 participants, animal studies, letters to the editor, historic reviews and unpublished data were excluded.

Search strategy
The authors (AU, KA and FJ) searched the MEDLINE-PubMed database of the National Library of Medicine, National Institutes of Health, Bethesda, Maryland for articles addressing the focused question.

Search limits were set to include articles published from January 1999 up to and including July 2012. The search algorithm used was: (bisphosphonates OR bisphosphonate OR di-phosphonate) AND (extraction*) AND (dental OR tooth) AND (metastatic) AND (cancer) AND (osteonecrosis). "Osteonecrosis" and "tooth extraction" were the MeSH search terms used.

The initial search yielded 360 studies (Figure 1). The authors independently read the titles and abstracts of these articles in order to identify the relevant studies.

Information was extracted from studies that fulfilled the eligibility criteria and entered into a spreadsheet.

These studies were then further analyzed individually by the authors so that an agreement on the inclusion of each study in this review could be reached.

Total subject populations, subjects developing BRONJ and subjects with a history of dental extractions were pooled and the mean weighted prevalence was calculated.

In total, 22 studies (10, 13-33) were included. Of these, 18 studies (10, 13-17, 19-23, 25, 27, 29-33) provided positive evidence linking dental extractions and BRONJ in multiple myeloma, breast cancer and prostate cancer patients (Table 1), whereas 4 studies (18, 24, 26, 28) did not show an association between dental extractions and the onset of BRONJ (Table 2).
Table 1 : Prevalence of BRONJ and dental extractions in cancer patients taking BPs

<table>
<thead>
<tr>
<th>Investigators, year</th>
<th>Study design</th>
<th>Type of BP and route of administration</th>
<th>Duration of use (median)</th>
<th>Total subjects</th>
<th>BRONJ subjects</th>
<th>Extractions</th>
<th>Multiple myeloma (Prevalence of BRONJ)</th>
<th>Breast cancer (Prevalence of BRONJ)</th>
<th>Prostate cancer (Prevalence of BRONJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamias et al., 2005 (14)</td>
<td>P</td>
<td>Zoledronate, Pamidronate, Ibandronate, IV</td>
<td>4-86 M (20)</td>
<td>252</td>
<td>17</td>
<td>13</td>
<td>9.9%</td>
<td>2.9%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Sanna et al., 2005 (27)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>14-48 M (30)</td>
<td>81</td>
<td>10</td>
<td>4</td>
<td>12.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badros et al., 2006 (13)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>7 M 14 Y</td>
<td>340</td>
<td>22</td>
<td>10</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimopoulos et al., 2006 (19)</td>
<td>P</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>4-123 M (29)</td>
<td>202</td>
<td>15</td>
<td>10</td>
<td>7.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zervas et al., 2006 (33)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>4-120 M (24)</td>
<td>254</td>
<td>28</td>
<td>13</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jadu et al., 2007 (23)</td>
<td>R</td>
<td>Pamidronate, IV</td>
<td>NA</td>
<td>655</td>
<td>24</td>
<td>15</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortega et al., 2007 (25)</td>
<td>R</td>
<td>Zoledronate, IV</td>
<td>1-41 M (7)</td>
<td>52</td>
<td>6</td>
<td>3</td>
<td>11.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boonyapakorn et al., 2008 (15)</td>
<td>P</td>
<td>Zoledronate, Pamidronate, Ibandronate, IV</td>
<td>6-101 M (27)</td>
<td>80</td>
<td>22</td>
<td>17</td>
<td>46%</td>
<td>23%</td>
<td>5%</td>
</tr>
<tr>
<td>Cafro et al., 2008 (16)</td>
<td>R</td>
<td>Zoledronate, IV</td>
<td>1-81 M (23)</td>
<td>105</td>
<td>17</td>
<td>11</td>
<td>16.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estilo et al., 2008 (20)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>10-100 M (29)</td>
<td>310</td>
<td>28</td>
<td>14</td>
<td>21.4%</td>
<td>64.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Hoff et al., 2008 (10)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>1-72 M (24)</td>
<td>3994</td>
<td>29</td>
<td>16</td>
<td>2.4%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Ibrahim et al., 2008 (22)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>1-65 M (10)</td>
<td>539</td>
<td>8</td>
<td>4</td>
<td>3.4%</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Walter et al., 2008 (32)</td>
<td>CS</td>
<td>Zoledronate, IV</td>
<td>3-12 M</td>
<td>43</td>
<td>8</td>
<td>7</td>
<td>18.6%</td>
<td>18.6%</td>
<td></td>
</tr>
<tr>
<td>Cetiner et al., 2009 (17)</td>
<td>R</td>
<td>Zoledronate, IV</td>
<td>5-76 M (27)</td>
<td>32</td>
<td>5</td>
<td>4</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fehm et al., 2009 (21)</td>
<td>R</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>1-77 M (13)</td>
<td>233</td>
<td>10</td>
<td>6</td>
<td>4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vahtsevanos et al., 2009 (29)</td>
<td>LC</td>
<td>Zoledronate, Pamidronate, Ibandronate, IV</td>
<td>5-68 M (27)</td>
<td>1621</td>
<td>80</td>
<td>46</td>
<td>8.5%</td>
<td>3.1%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Walter et al., 2009 (30)</td>
<td>R</td>
<td>Zoledronate, Clodronate, Pamidronate, Ibandronate, IV</td>
<td>16-74 M (42)</td>
<td>75</td>
<td>4</td>
<td>2</td>
<td>5.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P, prospective R, retrospective LC, longitudinal cohort CS, cross-sectional M, month Y, year NA, not available
Table 1: Prevalence of BRONJ and dental extractions in cancer patients taking BPs (continue)

<table>
<thead>
<tr>
<th>Investigators, year</th>
<th>Study design</th>
<th>Type of BP and route of administration</th>
<th>Month Duration of use (median)</th>
<th>Total subjects</th>
<th>BRONJ subjects</th>
<th>Examinations</th>
<th>Multiple myeloma (Prevalence of BRONJ)</th>
<th>Breast cancer (Prevalence of BRONJ)</th>
<th>Prostate cancer (Prevalence of BRONJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walter et al., 2010 (31)</td>
<td>R (I)</td>
<td>Zoledronate, Pamidronate, Ibandronate, IV</td>
<td>27-128 M (64)</td>
<td>81</td>
<td>4</td>
<td>4</td>
<td>4.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CS (II)</td>
<td>Zoledronate, Pamidronate, Ibandronate, IV</td>
<td>4-55 M (24)</td>
<td>78</td>
<td>16</td>
<td>10</td>
<td>20.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R, retrospective CS, cross-sectional M, month

Table 2: Studies reporting a low prevalence of BRONJ in subjects taking BPs

<table>
<thead>
<tr>
<th>Investigators, year</th>
<th>Aim</th>
<th>Study design</th>
<th>Type of BP and route of administration</th>
<th>Month Duration of use (median)</th>
<th>Total subjects</th>
<th>BRONJ subjects</th>
<th>Examinations</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chahine et al., 2008 (18)</td>
<td>To analyze the frequency of BRONJ in children treated with pamidronate undergoing tooth extraction</td>
<td>R</td>
<td>Pamidronate, IV</td>
<td>3-1-08 (55)</td>
<td>278</td>
<td>0</td>
<td>113</td>
<td>No case of BRONJ was seen despite risk factors including dental extraction</td>
</tr>
<tr>
<td>Schwartz et al., 2008 (28)</td>
<td>To assess the risk of BRONJ in children taking BPs after dental extractions</td>
<td>R</td>
<td>Pamidronate, IV</td>
<td>24-108</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>No subject developed BRONJ</td>
</tr>
<tr>
<td>Lodi et al., 2010 (24)</td>
<td>To test the effectiveness of a new protocol in reducing BRONJ after tooth extraction</td>
<td>P</td>
<td>Zoledronate, Pamidronate, Clodronate, IV</td>
<td>3-36 (18)</td>
<td>23</td>
<td>0</td>
<td>23</td>
<td>Infection control can reduce BRONJ after tooth extraction in subjects treated with IV bisphosphonates</td>
</tr>
<tr>
<td>Saia et al., 2010 (26)</td>
<td>To evaluate the occurrence of BRONJ after surgical tooth extraction in subjects taking BPs</td>
<td>C</td>
<td>Zoledronate, Pamidronate, IV</td>
<td>≥36</td>
<td>60</td>
<td>5</td>
<td>60</td>
<td>BRONJ rarely developed in BP users who underwent surgical extraction</td>
</tr>
</tbody>
</table>

P, prospective R, retrospective C, cohort

Results

Characteristics of the selected publications

No RCTs addressing the focused questions could be identified. The overall level of evidence according to the ABC scale proposed by HADORN et al. (34) was Level B. This category is comprised of poorly controlled or uncontrolled studies, observations/studies with high potential for bias (case series with comparison to historical controls), case series or case reports, conflicting evidence with more support. All retrospective and prospective studies identified...
in this review analyzed data pertaining to the treatment of individuals at academic or research institutions. The characteristics of studies that fulfilled the individual selection criteria for the questions being addressed are discussed.

**Dental extractions and BRONJ in cancer patients**

Eighteen studies (10, 13-17, 19-23, 25, 27, 29-33) addressed the relationship between BRONJ and dental extractions in cancer patients (Table 1). Of these, there were 12 retrospective studies (10, 13, 16, 17, 20-23, 25, 27, 30, 33), 3 prospective studies (14, 15, 19), 1 cross-sectional study (32), 1 longitudinal cohort study (29) and 1 combined study with retrospective and cross-sectional components (31).

All studies reported that subjects were taking either IV zoledronate or pamidronate. The average duration of bisphosphonate administration prior to the onset of BRONJ symptoms was 26.4 (± 13.6) months. The combined total number of subjects in all the studies was 9027, of which 6437 were divided between the multiple myeloma (n = 3097), breast cancer (n = 3108) and prostate cancer (n = 232) groups. Of these, 354 cancer patients developed BRONJ symptoms (5.5%). Two hundred and nine cancer patients with BRONJ symptoms (3.25%) had a positive history of recent dental extractions (Table 3). Four studies (18, 24, 26, 28) did not find an association between the onset of BRONJ symptoms and a history of dental extraction (Table 2). The average duration of bisphosphonate administration in these reports was 36 months. A longitudinal cohort study reported that 92% of the subjects taking BPs had no clinical or radiologic signs of BRONJ, 12 months following surgical tooth extraction (26). Analyzing the subsets of cancer patients, there were 3097 (48.1%) with multiple myeloma, 3108 (48.3%) with breast cancer and 232 (3.6%) with prostate cancer out of the total population of 6437 individuals (Table 1).

**Discussion**

We did not find any RCTs or meta-analyses in the literature addressing the relationship between dental extractions and BRONJ. Earlier studies suggesting the role played by dental extractions in exacerbating BRONJ have now paved the way for an emerging trend to avoid the complication as much as possible. Expert panels constituted by the American Dental Association (35), American Society for...
Bone and Mineral Research (6) and American Association of Oral and Maxillofacial Surgeons (36) have issued guidelines over the past few years for managing individuals taking BPs; however, a consensus regarding the management of BRONJ has failed to emerge. A recent case control study, for instance, advocates the use of Plasma Rich in Growth Factor (PRGF) to reduce the risk of BRONJ in IV-BP patients undergoing dental extractions (37).

Overall, the underlying theme of most BRONJ management protocols is the reduction of potential sources of infection, be it by antibiotic therapy or by surgical interventions aimed at complete wound closure.

LODI et al. (24) proposed a protocol for the prevention of BRONJ in cancer patients taking IV BPs, which involves the reflection of a full-thickness muco periosteal flap. This technique reduced the incidence of BRONJ in the prospective study, even though it inflicted trauma to periodontal tissues.

SAIA et al. (26) recently conducted a study to evaluate the incidence of BRONJ following surgical tooth extraction, and reported a low occurrence of the condition. These reports should be considered preliminary until the safety and efficacy of the mentioned protocols are validated by randomized controlled trials.

With a positive history of dental extractions, the prevalence of BRONJ in subjects with osteoporosis was reported to increase to 0.34-0.09% (12). On the other hand, based on the reports included in this review, cancer patients have a greater predisposition for developing BRONJ (5.5 ± 3.93%) even though the number of BP prescriptions in this high-risk group are fewer in comparison to osteoporosis patients (36). Based on the local and systemic risk factors, subjects who are potential candidates for dental extractions can be placed in low, medium or high risk groups for developing BRONJ and a detailed algorithm that can serve as a ready guide for clinicians has recently been proposed (38).

Discontinuation of BP therapy prior to dental surgical procedures in subjects-at-risk for developing BRONJ has been highly debated over the years (3, 39).

The American Association of Oral and Maxillofacial Surgeons (36) recommends discontinuation of bisphosphonate therapy for 3 months prior to extractions in patients who have taken an oral bisphosphonate for less than three years with concomitant corticosteroids.

If patients have taken an oral bisphosphonate for more than three years with/without any concomitant steroid medication, discontinuation of the oral bisphosphonate for three months prior to oral surgery should be considered if systemic conditions permit. This is followed by cessation of the drug until osseous healing is observed. However, due to the fact that BPs have a long half-life, this "drug-holiday" might not be helpful (40). It may, in fact, expose subjects to oncologic complications. The decision should thus be made by the treating oncologist after carefully considering the risks involved (41).

As the pathogenesis of BRONJ is not entirely understood yet, preventive guidelines to combat its onset largely rely on available evidence in the literature. A recommendation to physicians is to routinely refer cancer patients to dentists or oral surgeons familiar with the early presenting signs of BRONJ whenever BP therapy is being considered.

At this stage, all operative and surgical dental procedures, including extraction of non-restorable teeth and restorations should be carried out by the dentist. Thereafter, upon commencement of BP therapy, instructions given by the
dentist on improving and maintaining oral hygiene can go a long way in reducing the risk of BRONJ. An added advantage of meticulous oral hygiene in patients taking BPs is that it helps prevent the secondary infection of exposed, necrotic bone in the oral cavity, which has been shown to be a cause for concern (42). If adopted, these measures are sure to decrease the overall prevalence of BRONJ cases.

It is important that the results of the current study are viewed in the context of the study design that was utilized. The dearth of prospective randomized controlled trials makes generalization of the causal relationships observed in this study rather difficult, and should thus be approached with caution.

**Conclusion**

There is a plausible relationship between dental extractions and the development of BRONJ in cancer subjects; therefore, written informed consent must be obtained prior to dental procedures in cancer subjects at risk for developing BRONJ. Additional research particularly randomized controlled trials (RCTs) and meta-analyses are required to assess the role of dental extraction in cancer subjects taking BPs for prolonged periods.

**References**


37. MOZZATI M, ARATA V, GALLESIO G. Tooth extraction in patients on zoledronic acid therapy. Oral Oncol. 48, 817 (2012).