A Rational Approach to Dental Management of Patients on Bisphosphonates

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Abstract

There has been a lot of focus on osteonecrosis of the jaws associated with the usage of bisphosphonates both in dental and medical literature in recent years. However, the exact pathogenesis of bisphosphonate-related osteonecrosis of the jaws remains unclear. Against the background of emerging evidence of an evolving condition, it is not surprising that there is a lack of robust evidence-based recommendations on dental treatment of patients on bisphosphonates. This paper seeks to provide a rational approach to the dental management of patients on bisphosphonates based on current literature. [Singapore Dent J 2011;32(1):1–13]

Key Words: bisphosphonates, osteonecrosis

Introduction

Bisphosphonates are used to treat osteoporosis, multiple myeloma, metastatic neoplasms with skeletal involvement, Paget’s disease of bone, other metabolic bone diseases. Bisphosphonates come in intravenous (IV) and oral forms. IV bisphosphonates are used for multiple myeloma and metastatic neoplasms with skeletal involvement while the oral bisphosphonates are used mainly for osteoporosis. However, IV bisphosphonate (zoledronic acid) has recently been administered once yearly to treat osteoporosis.1 The pharmacologic characteristics and the usual dosing of the bisphosphonates are described in Table 1.

Bisphosphonates are analogues of inorganic pyrophosphates that have a high affinity for hydroxyapatite crystals.10,11 They are incorporated into the skeleton without being degraded and are remarkably persistent drugs. Aminobisphosphonates which contain nitrogen side chain have much higher potency and longer half-life compared to nonaminobisphosphonates. The estimated half-life for alendronate is up to 12 years.12 The potency of bisphosphonate is usually compared relative to etidronate which is the least potent non-nitrogen containing bisphosphonate. Zoledronic acid is the most potent of the group and is 10,000 more potent relative to etidronate. This is followed by pamidronate with relative potency of 1,000–5,000 and alendronate with relative potency of 1,000.

Mechanisms of Action of Bisphosphonate

Bisphosphonates are powerful inhibitors of osteoclast activity. They cause the induction of non-hydrolyzable adenosine triphosphate analogue that induces cellular apoptosis and inhibition of farnesyl diphosphonate synthase which disrupts cholesterol synthesis resulting in dysregulation of intracellular transport, cytoskeletal organization and cell proliferation. This leads to inhibition of osteoclast function, reduce osteoclast recruitment, and induce osteoblastic production of osteoclast-inhibiting factor.13–15
Bisphosphonate Related Osteonecrosis of Jaws

The first report which described bisphosphonate related osteonecrosis of jaws (BRONJ) was in 2003 by Marx.16 He observed painful exposed bone in mandible, maxilla or both jaws in 36 patients who were treated with intravenous bisphosphonates. Subsequently, more reports on bisphosphonate-associated osteonecrosis of jaws were published (Table 2). Yeo et al17 reported five cases of bisphosphonate-related osteonecrosis of the jaws in Singapore.

Pathogenesis of BRONJ

Despite the numerous publications, the pathogenesis of BRONJ remains elusive. It is obvious that in BRONJ the problem occurs in the bone but studies have indicated that the soft tissue of the oral mucosa may also be involved. It has been proposed that bisphosphonates, which accumulate in the bone, have direct toxic effects on the oral epithelium and inhibit normal healing of soft tissue lesions caused by either dental extractions or some other trauma.64,65 The failure of soft tissue to heal would result in the exposure of the bone, which then becomes necrotic.

There are a number of hypotheses associated with the pathogenesis of BRONJ.

Suppression of bone remodelling

Nearly every report on BRONJ alludes to bisphosphonate-induced bone remodeling suppression as a likely mechanism. Osteoclasts are the main cellular target of bisphosphonates and osteoclast-mediated bone remodeling is suppressed through disruption of intracellular pathways. It has been

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**Table 1. Characteristics of bisphosphonates available**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Nitrogen containing</th>
<th>Relative potency</th>
<th>Indication and usual dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate2</td>
<td>Oral</td>
<td>No</td>
<td>1</td>
<td>Paget’s disease: 5–20 mg/kg/day × 3–6 mo</td>
</tr>
<tr>
<td>Tiludronate3</td>
<td>Oral</td>
<td>No</td>
<td>50</td>
<td>Paget’s disease: 400 mg/day × 3 mo</td>
</tr>
<tr>
<td>Alendronate4</td>
<td>Oral</td>
<td>Yes</td>
<td>1,000</td>
<td>Osteoporosis treatment: 70 mg once/wk</td>
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<td></td>
<td>Osteoporosis prophylaxis: 35 mg once/wk</td>
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<td></td>
<td>Paget’s disease: 40 mg/day × 6 mo</td>
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<td></td>
<td>Osteoporosis treatment and prophylaxis: 35 mg once/wk</td>
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<td></td>
<td>Paget’s disease: 30 mg/day × 2 mo</td>
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<td></td>
<td>Osteoporosis treatment: 150 mg orally once/mo or intravenous 3 mg intravenously every 3 mo</td>
</tr>
<tr>
<td>Risedronate5</td>
<td>Oral</td>
<td>Yes</td>
<td>1,000</td>
<td>Hypercalcemia of malignancy: 60–90 mg × 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paget’s disease: 30 mg/day × 3 days</td>
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<td></td>
<td>Osteolytic bone metastases: 90 mg every 3–4 wks</td>
</tr>
<tr>
<td>Ibandronate6,7</td>
<td>Oral or intravenous</td>
<td>Yes</td>
<td>1,000</td>
<td>Hypercalcemia of malignancy: 4 mg × 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple myeloma/bone metastases: 4 mg every 3–4 wks</td>
</tr>
<tr>
<td>Pamidronate8</td>
<td>Intravenous</td>
<td>Yes</td>
<td>1,000–5,000</td>
<td>Paget’s disease: 5 mg × 1 dose</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Osteoporosis treatment: 5 mg once/yr</td>
</tr>
<tr>
<td>Zoledronic acid9</td>
<td>Intravenous</td>
<td>Yes</td>
<td>10,000</td>
<td>Hypercalcemia of malignancy: 4 mg × 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple myeloma/bone metastases: 4 mg every 3–4 wks</td>
</tr>
</tbody>
</table>
### Table 2. Summary of case reports and case series of bisphosphonate related osteonecrosis of the jaws

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>No. of patients</th>
<th>Sex (Male/Female)</th>
<th>Primary diagnosis</th>
<th>Sites of BRONJ</th>
<th>Cause of BRONJ</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ruggiero et al, 2004(^{18})</td>
<td>63</td>
<td>18(M)/45(F)</td>
<td>Myeloma (28) Breast cancer (21) Other malignancy (7) Osteoporosis (7)</td>
<td>Mandible (39) Maxilla (23) Both jaws (1)</td>
<td>Procedure (54) Spontaneous (9)</td>
<td>Zoledronic acid (9) Pamidronate &amp; zoledronic acid (13) Pamidronate (34) Alendronate (5) Risedronate (1) Alendronate &amp; zoledronic acid (1)</td>
</tr>
<tr>
<td>3. Migliorati et al, 2005(^{20})</td>
<td>18</td>
<td>4(M)/14(F)</td>
<td>Myeloma (3) Breast cancer (10) Other malignancy (4) Osteopenia (1)</td>
<td>Mandible (8) Maxilla (2) Both jaws (1) Not reported (7)</td>
<td>Procedure (7) Spontaneous (1) Oral trauma (1) Not reported (9)</td>
<td>Zoledronic acid (7) Pamidronate &amp; zoledronic acid (9) Zoledronic acid &amp; ibandronate (1)</td>
</tr>
<tr>
<td>4. Bamias et al, 2005(^{21})</td>
<td>17</td>
<td>10(M)/7(F)</td>
<td>Myeloma (11) Breast cancer (2) Other malignancy (4)</td>
<td>Mandible (14) Maxilla (3)</td>
<td>Procedure (13) Spontaneous (2) Dentures (2)</td>
<td>Zoledronic acid (3) Pamidronate &amp; zoledronic acid (5) Pamidronate (4) Zoledronic acid (4) Pamidronate &amp; zoledronic acid (3) Pamidronate (4)</td>
</tr>
<tr>
<td>5. Pires et al, 2005(^{22})</td>
<td>12</td>
<td>3(M)/9(F)</td>
<td>Myeloma (4) Breast cancer (6) Other malignancy (2)</td>
<td>Mandible (8) Maxilla (3) Both jaws (1)</td>
<td>Procedure (8) Not reported (4)</td>
<td>Zoledronic acid (3) Pamidronate &amp; zoledronic acid (5) Pamidronate (4) Zoledronic acid (4) Pamidronate &amp; zoledronic acid (3) Pamidronate (4)</td>
</tr>
<tr>
<td>6. Melo et al, 2005(^{23})</td>
<td>11</td>
<td>7(M)/4(F)</td>
<td>Myeloma (7) Breast cancer (3) Other malignancy (1)</td>
<td>Mandible (8) Maxilla (2) Both jaws (1)</td>
<td>Procedure (9) Spontaneous (1) Dentures (1)</td>
<td>Zoledronic acid (11) Pamidronate &amp; zoledronic acid (3) Pamidronate (4) Alendronate (5)</td>
</tr>
<tr>
<td>7. Farrugia et al, 2006(^{24})</td>
<td>23</td>
<td>7(M)/16(F)</td>
<td>Myeloma (9) Breast cancer (6) Other malignancy (3) Osteoporosis (4) Paget’s disease (1)</td>
<td>Mandible (12) Maxilla (10) Both jaws (1)</td>
<td>Procedure (9) Spontaneous (14)</td>
<td>Zoledronic acid (11) Pamidronate &amp; zoledronic acid (3) Pamidronate (4) Alendronate (5)</td>
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</tbody>
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<thead>
<tr>
<th>Study, year (Reference)</th>
<th>No. of patients</th>
<th>Sex (Male/Female)</th>
<th>Primary diagnosis</th>
<th>Sites of BRONJ</th>
<th>Cause of BRONJ</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Thakkar et al, 200625</td>
<td>17</td>
<td>13 (M)/4 (F)</td>
<td>Myeloma (15)</td>
<td>Not reported (7)</td>
<td>Procedure (3)</td>
<td>Zoledronic acid (7)</td>
</tr>
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<td></td>
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<td></td>
<td>Other malignancy (2)</td>
<td></td>
<td></td>
<td>Pamidronate &amp; zoledronic acid (6)</td>
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<td></td>
<td>Pamidronate (4)</td>
</tr>
<tr>
<td>9. Wutzl et al, 200626</td>
<td>17</td>
<td>8 (M)/9 (F)</td>
<td>Myeloma (12)</td>
<td>Mandible (9)</td>
<td>Procedure (13)</td>
<td>Zoledronic acid (11)</td>
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<td></td>
<td></td>
<td></td>
<td>Breast cancer (4)</td>
<td>Maxilla (8)</td>
<td></td>
<td>Pamidronate &amp; zoledronic acid (2)</td>
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<td></td>
<td></td>
<td></td>
<td>Other malignancy (1)</td>
<td></td>
<td>Spontaneous (4)</td>
<td>Pamidronate (4)</td>
</tr>
<tr>
<td>10. Graziani et al, 200627</td>
<td>14</td>
<td>1 (M)/13 (F)</td>
<td>Breast cancer (11)</td>
<td>Mandible (6)</td>
<td>Procedure (9)</td>
<td>Zoledronic acid (14)</td>
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<td></td>
<td></td>
<td>Other malignancy (3)</td>
<td>Maxilla (7)</td>
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<td>Pamidronate (12)</td>
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<td></td>
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<td></td>
<td>Both jaws (1)</td>
<td>Spontaneous (5)</td>
<td></td>
</tr>
<tr>
<td>11. Zarychanski et al, 200628</td>
<td>12</td>
<td>7 (M)/5 (F)</td>
<td>Myeloma (10)</td>
<td>Mandible (10)</td>
<td>Procedure (7)</td>
<td>Pamidronate (12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast cancer (1)</td>
<td>Maxilla (1)</td>
<td></td>
<td>Pamidronate &amp; zoledronic acid (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other malignancy (1)</td>
<td>Both jaws (1)</td>
<td>Spontaneous (3)</td>
<td>Pamidronate, zoledronic acid &amp; ibandronate (1)</td>
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<td></td>
<td></td>
<td></td>
<td>Tooth abscess (1)</td>
<td></td>
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<tr>
<td>12. Dimitrakopoulos et al, 200629</td>
<td>11</td>
<td>5 (M)/6 (F)</td>
<td>Myeloma (5)</td>
<td>Mandible (7)</td>
<td>Procedure (7)</td>
<td>Zoledronic acid (6)</td>
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<td>Other malignancy (6)</td>
<td>Maxilla (3)</td>
<td></td>
<td>Pamidronate &amp; zoledronic acid (4)</td>
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<td>Both jaws (1)</td>
<td>Spontaneous (3)</td>
<td>Pamidronate, zoledronic acid &amp; ibandronate (1)</td>
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<td>Dentures (1)</td>
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<td>Breast cancer (1)</td>
<td>Maxilla (6)</td>
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<td>Pamidronate &amp; zoledronic acid (8)</td>
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<td></td>
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<td></td>
<td>Other malignancy (2)</td>
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<td>Spontaneous (10)</td>
<td>Pamidronate (10)</td>
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<td>Osteoporosis (2)</td>
<td></td>
<td>Not reported (4)</td>
<td>Alendronate (2)</td>
</tr>
<tr>
<td>14. Dannemann et al, 200731</td>
<td>23</td>
<td>12 (M)/11 (F)</td>
<td>Myeloma (10)</td>
<td>Mandible (17)</td>
<td>Procedure (21)</td>
<td>Zoledronic acid (14)</td>
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<td>Breast cancer (7)</td>
<td>Maxilla (4)</td>
<td></td>
<td>Pamidronate &amp; zoledronic acid (5)</td>
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<td></td>
<td></td>
<td>Other malignancy (3)</td>
<td>Both jaws (2)</td>
<td>Oral ulcer (1)</td>
<td>Pamidronate (1)</td>
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<td>Osteoporosis (3)</td>
<td></td>
<td>Oral prosthesis (1)</td>
<td>Alendronate (3)</td>
</tr>
<tr>
<td>15. Diego et al, 200732</td>
<td>10</td>
<td>6 (M)/4 (F)</td>
<td>Myeloma (2)</td>
<td>Mandible (6)</td>
<td>Procedure (10)</td>
<td>Zoledronic acid (10)</td>
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<td></td>
<td>Breast cancer (1)</td>
<td>Maxilla (3)</td>
<td></td>
<td>Pamidronate (12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other malignancy (7)</td>
<td>Both jaws (1)</td>
<td>Spontaneous (12)</td>
<td>Pamidronate (12)</td>
</tr>
<tr>
<td>16. Summary of studies with fewer than</td>
<td>102</td>
<td>39 (M)/63 (F)</td>
<td>Myeloma (41)</td>
<td>Mandible (60)</td>
<td>Procedure (83)</td>
<td>Zoledronic acid (45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast cancer (27)</td>
<td>Maxilla (31)</td>
<td></td>
<td>Pamidronate &amp; zoledronic acid (21)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Pamidronate (21)</td>
</tr>
</tbody>
</table>
A rational approach to dental management of patients on bisphosphonates

shown that the intracortical remodeling rates of the jaws are 10–20 times higher than that of the iliac crest.\textsuperscript{66,67} This hypothesis suggests bisphosphonate activity may be excessive in the metabolically active jaws leading to bone necrosis which quickly becomes exposed bone when the thin overlying mucosa breaks down due to minor trauma or dental extractions.

Suppression of bone vasculature

Before the emergence of BRONJ, much of what was known concerning osteonecrosis centered on the two following conditions that manifest as a result of disruption of the vasculature. They are avascular necrosis of the hip and osteoradionecrosis. Avascular necrosis of the hip occurs as a result of disruption of the vasculature.\textsuperscript{68} Similarly, osteoradionecrosis, most prominently of the jaw, occurs after radiation-induced disruption of the vasculature.\textsuperscript{69–71} The existence of these conditions, and the clear role of disrupted vasculature in their pathophysiology, has led to the hypothesis that the vasculature plays a similar role in the pathophysiology of BRONJ. Numerous studies have documented antiangiogenic effects of bisphosphonates \textit{in vitro}.\textsuperscript{72,73} However, there have been no studies assessing the vascular pattern in BRONJ.

Infection as a contributory factor

It is believed that infection could contribute to BRONJ by enhancing osteoclast-independent bone resorption. Typically, the exposed bone is secondarily infected by \textit{Actinomyces} species and other microflora in the oral cavity. BRONJ tissue consistently shows a prevalence of scalloped bone surface,\textsuperscript{69,74,75} a seemingly paradoxical feature, given the suppressive effect of bisphosphonates on bone resorption. Bacteria and associated fibroblast-like cells have the capacity to directly resorb bone independent of osteoclasts by liberating various acids and proteases.\textsuperscript{76–78} Because osteoclasts signal osteoblasts during normal bone remodeling,\textsuperscript{79,80} resorption that occurs independent of osteoclasts would likely lack osteoblast-mediated bone formation. Such resorption could factor into the pathogenesis of BRONJ.

Pathophysiological cofactors

Various cofactors are associated with BRONJ such as comorbidities (e.g. diabetes\textsuperscript{81}), lifestyle...
factors (e.g. smoking and obesity), interventions (e.g. dental extraction), and concurrent medications (e.g. corticosteroids) have all been associated with BRONJ. These cofactors individually do not cause bone necrosis of the jaws but in the presence of bisphosphonates play a significant role in the pathophysiology of BRONJ.

Incidence of BRONJ

The incidence of BRONJ with intravenous bisphosphonate ranges from 0.8% to 12%. Oral bisphosphonate is associated with lower incidence of BRONJ ranging from 0.01% to 0.04%. This increases to 0.09%–0.34% following extractions.

Radiologic Finding of BRONJ

The radiologic findings of BRONJ are not specific and mimic other conditions such as osteomyelitis, osteoradionecrosis, cancer metastasis and Paget’s disease. Periapical radiograph and orthopantomogram findings include thickening of the lamina dura, osteolysis, diffuse sclerosis, narrowing of the mandibular canal and poor healing or non-healing of extraction sites.

Definition and Staging of BRONJ

There are various names to this condition. The American association of oral and maxillofacial surgeons refer this type of osteonecrosis as “bisphosphonate related osteonecrosis of the jaws” and the Academy of Oral Medicine refers this as “bisphosphonate-associated osteonecrosis of the jaws”. Marx prefers to call this condition as “bisphosphonate-induced osteonecrosis of the jaws”.

In this article, we will use the definition proposed by the American Association of Oral and Maxillofacial surgeons. BRONJ is defined as the exposed necrotic bone in the maxillofacial region that has persisted for more than eight weeks in patients with current or previous treatment with a bisphosphonate and with no history of radiation therapy to the jaws. It is a serious and debilitating condition affecting the jaws.

There are four stages of BRONJ, which are as follows:

Stage 0 defines signs and symptoms short of exposed necrotic bone in patients that might indicate a histological necrosis or a prenecrotic state.

Stage 1 defines exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.

Stage 2 defines exposed/necrotic bone in patients with pain and clinical evidence of infection.

Stage 3 defines exposed/necrotic bone in patients with pain, infection and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border.

Strategy for Management of Patients on Bisphosphonates

Identification of patients at risk of BRONJ

It appears that certain patients are more at risk of BRONJ development. Low risk patients can be treated in general dental practice settings while high risk patients may be referred to an oral and maxillofacial surgeon or dental specialist who has experience in managing such patients.

High-risk patients include:

- Cancer patients on intravenous bisphosphonate
- Patients on bisphosphonate therapy with exposure to chemotherapeutic agents (i.e. cyclophosphamide, erythropoietin, thalidomide and steroids)
- Patients on oral bisphosphonate for more than 3 years
- Patients on bisphosphonate and smoking
- Patients on bisphosphonate and other systemic medical conditions (i.e. cancer, diabetes, obesity, atherosclerotic heart disease)

Prevention of BRONJ

Prior to bisphosphonate therapy

A preventive regime should be instituted for patients who are about to start intravenous bisphosphonates for oncologic reasons. The dentition is assessed for carious lesions, defective restorations, vitality and periapical lesions. The
periodontium (pocketing, furcation involvement, bleeding on probing, suppuration, mobility) is also examined. The patient’s oral hygiene (plaque, calculus accumulation) is recorded. Oral mucosa and alveolar processes are checked for infection, ulcerations, hyperplasia, bony spicules and exostoses. If patients are edentulous or partially edentulous with removable prostheses, the prostheses are checked for fit, retention, stability and hygiene. Ill-fitting dentures can cause trauma and ulcerations to the oral mucosa and initiate BRONJ.

Baseline dental radiographs in forms of orthopanograms, bitewings, selective periapical radiographs are required for the detection of occult caries and any other pathology, such as cysts, buried teeth or roots.

Dental clearance involves the treatment of active oral infections, elimination of sites at high risk for infection (e.g. removal of partially impacted wisdom teeth, unsalvageable teeth, non-restorable teeth, teeth with substantial periodontal bone loss). Removal of tori and bony exostoses are indicated especially when patients are wearing or will be wearing removable prostheses as these are sites at risk of bone exposure and initiation of BRONJ. Ill-fitting dentures are adjusted and fabrication of new dentures may be indicated if existing dentures are beyond salvage. It is important that the new dentures do not cause mucosal ulcerations.

All invasive dental procedures should be completed prior to the start of intravenous bisphosphonate. Bisphosphonate therapy should be delayed, if systemic condition permits, until the extraction site has epithelialized (14–21 days) or until there is adequate osseous healing. After the initial dental clearance, it is important to provide routine dental care afterwards. It is advisable to perform oral examination and dental cleaning six monthly. Constant surveillance of the oral cavity is important to detect any bone exposure so that it can be treated early. Oral hygiene in forms of tooth brushing, flossing and rinsing with fluoride-containing mouth rinses, are reinforced. Diet counseling in patient with high caries risk, patient education and motivation are important to prevent future caries and periodontal diseases development and progression in the remaining dentition. All these non-invasive dental procedures can be carried out in general dental practice setting.

**Currently on bisphosphonate therapy**

For patients who are already on intravenous bisphosphonates, maintenance and conservative dental care are performed as far as possible. Conservative measures remain the treatment of choice in order to avoid dentoalveolar surgery, periodontal surgery and extractions if possible to reduce the risk of BRONJ development. Non-restorable teeth can be treated by decortication and endodontic treatment.

Patients who are receiving oral bisphosphonate therapy, routine dental care is encouraged. Elective dentoalveolar surgery and extractions are not contraindicated, provided the necessary precautions are taken. For patients on oral bisphosphonate therapy for more than 3 years with or without concomitant steroid medication, discontinuation of oral bisphosphonate 3 months prior to oral surgery should be considered in consultation with the prescribing physician if the systemic condition permits and resumed after osseous healing has occurred. Patients with concomitant steroid medication are known to be at a slightly higher risk of BRONJ and should be informed accordingly.

For patients on oral bisphosphonate therapy less than 3 years without concomitant steroid medication and have no clinical risk factors, dentoalveolar surgery and extractions can proceed without any alterations. For patients on oral bisphosphonate therapy less than 3 years with concomitant steroid medication, a 3-month drug holiday should be considered, in consultation with the prescribing physician.

**Biochemical test to assess risk for BRONJ in patient on bisphosphonate**

Biochemical bone turnover markers are released during bone remodeling and can provide a measure of the rate of bone metabolism. One of these bone turnover markers is serum C-terminal telopeptide (CTX). Serum CTX measures the serum level of the C-terminal telopeptide-related fragment from a cross-linking chain in type I collagen, which is cleaved by the osteoclast in bone resorption. CTX is a measure of the bone resorption activity and is used as a predictor of bone mineral density (BMD) response to bisphosphonate therapy.99 Marx and Ranjit100,101 reported the use of CTX in predicting the risk of BRONJ related to oral
bisphosphonate use. Marx studied a series of 30 patients who were on oral bisphosphonate therapy and correlated them with their serum CTX. He concluded that patients with serum CTX less than 100 pg/mL representing high risk of BRONJ, values between 100 and 150 pg/mL representing moderate risk and values above 150 pg/mL representing minimal risk. Further validation studies are required. As its reliability remains controversial the American Association of Oral and Maxillofacial Surgeons position paper did not include the use of CTX on the management of bisphosphonate-related osteonecrosis of the jaws.

Management of BRONJ

The treatment goals of established BRONJ are to eliminate pain, control infection of the soft and hard tissues and minimise the progression or occurrence of bone necrosis.

Patient with BRONJ stage 0
The management of stage 0 patients is essentially preventive and avoids invasive oral surgical procedures and dental extractions as far as possible.

Patient with BRONJ stage 1
The management of stage 1 patients is mainly conservative. It includes oral antibacterial mouth rinse, adjustment of dentures to minimise soft tissue trauma or irritation, patient education, regular quarterly follow-up. Long-term discontinuation of bisphosphonate should be considered if the patient’s systemic condition permits after discussing with prescribing physician.

Patient with BRONJ stage 2
The treatment of stage 2 patients includes the use of oral antibacterial mouth rinse, analgesia for pain control, superficial debridement and removal of loose sequestrum to relieve soft tissue irritation with minimal disruption to adjacent soft tissue and underlying bone and antibiotic therapy for the superinfection. Cultures, including those for aerobic and anaerobic bacteria may be collected to determine the appropriate antimicrobial intervention. The possibility of long-term discontinuation of bisphosphonate if systemic condition permits should be considered after consulting with the prescribing physician. The infection is usually treated with empirical broad-spectrum oral antibiotics such as penicillin V or amoxicillin. If patient is allergic to penicillin, clindamycin can be used. Other alternative antibiotics include erythromycin ethylsuccinate, doxycycline together with metronidazole, levofloxacin and moxifloxacin. Once the culture and sensitivity result is available, specific antibiotic therapy should be instituted.

Patient with BRONJ stage 3
The management of stage 3 patients is essentially similar to that of stage 2 patients. More aggressive surgical debridement or resection to achieve longer term palliation of infection and pain may be necessary. The effectiveness of hyperbaric oxygen therapy is still undetermined.

Examples of Local Cases With BRONJ

Case 1
A 60 year-old Chinese female presented with non-healing socket over upper right canine region of 4-month duration. She also complained of recurrent epitaxis from the right nose. ENT examination was unremarkable. She was diagnosed with osteoporosis and has been on oral alendronate (Fosamax) for the past 4 years.

Clinical examination revealed sinus tract over upper right canine region (Figure 1). Anterior maxillary occlusal showed radiolucent defect over the above region (Figure 2).

Fosamax was discontinued. She underwent surgical debridement and exploration under local anaesthesia. Figure 3 showed sequestrum with defect from alveolar ridge to right piriform rim. Tissues were submitted for histology and results showed sequestrum which is consistent with BRONJ given the medical history. She was reviewed and the region healed uneventfully 1 year later.

Case 2
A 59 years-old Malay female with medical history of breast cancer with bone metastasis presented with stage II BRONJ over left lower posterior ridge. She developed 3 mm of exposed bone after eight doses of IV bisphosphonate zoledronic acid (Zometa) and oral chemotherapy. IV bisphosphonate was discontinued and BRONJ
Case 3
A 45-year-old Chinese female with medical history of breast cancer with bone metastasis presented with exposed bone and multiple sinus tracts over the right maxilla. She was treated with IV bisphosphonate zoledronic acid (Zometa). She was diagnosed with stage III BRONJ over the right maxilla (Figure 6) and was not responsive to conservative treatment. Right maxillectomy was performed to alleviate pain for the patient. Figure 7 showed the resected right maxillary bone sequestrum.

Conclusion
Patients on bisphosphonate therapy may develop BRONJ which is a rare but debilitating condition.
BRONJ is difficult to treat and patients may even require jaw resection to palliate the infection and pain. Therefore, it is important for the dental community to be familiar with the management of these patients in collaboration with our medical colleagues.

References

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