BISPHOSPHONATES: Importance in oral surgery

Carlos Madrid

Service de Stomatologie et de médecine dentaire
Policlinique Médicale Universitaire
Département Universitaire de Médecine et Santé Communautaire
Université de Lausanne
Update 2009 – Aims

- Bisphosphonate without osteonecrosis
- Bisphosphonates with ON
- Incidence
- Pathogenesis & risk factors
- Dosing effect

- Oral BPs & Osteoporosis main problem today in terms of
  - Level of prevention
  - Surgical approach of patients.
  - Introduction of once-yearly IV 5mg zoledronic acid to prevent SRE in severe osteopenia/osteoporosis
- Investigations
- Treatment
- Future
Bisphosphonates without ON

- potent osteoclast inhibitors
- first choice therapy in diseases affecting bone metabolism
  - osteoporosis
  - Paget’s disease,
  - malignant tumors
- a highly selective deposition in bone due to a high affinity interaction between the BPs molecular structure and the hydroxyapatite crystals (Rogers et al. 2000).
- Once deposited in bone, very small amounts are released into the circulation during bone turnover.
- the half-life of BPs in bone is estimated in years (Lin 1996).
BPs. : oral administration, few weeks of intake, adequate levels of bone resorption inhibition observed.

These dosages insufficient to counterbalance the resorptive activities of bone metastatic tumors.

In these situations : intravenous BPs

The high resorptive process can be halted in 24 - 48 hours. Table 1 shows the main BPs with their chemical structure, relative potency and used route of administration.
Bisphosphonate and periodontal diseases

- an adjunctive host-modulating therapy in the treatment of periodontal diseases.
- biweekly IV-alendronate at a concentration of 0.05mg/kg could retard bone loss around affected teeth in comparison to controls (Brunsvold et al. 1992).
- a course of 3mg/kg of alendronate showed a significant reduction in bone loss (Reddy et al. 1995).
- in humans using clinical and radiographic outcome variables demonstrated a significant decrease in the proportion of teeth with alveolar bone loss at 9 months after use of alendronate (Reddy et al. 2003, Rocha et al. 2001).
- A 2 years clinical trial using 70 mg alendronate once-weekly in patients with moderate or severe periodontal disease (Jeffcoat 2006).
- a significant gain in alveolar bone height was demonstrated in the alendronate group in comparison to the placebo. No side effect
Bisphosphonate and implants

- In order to avoid the systemic administration of BPs and the use of such high doses,
- topical application of BPs has been investigated in experimental models (Peter et al. 2005, Peter et al. 2006).
- BPs specifically bind to hydroxyapatite (HA), implants coated with HA or other calcium coating have been used in this investigations (Kajiwara et al. 2005, Peter et al. 2005).
- These BP-coated implants have demonstrated a high concentration of BPs in the first 20 μm of bone around the implant promoting osteogenesis at the bone tissue/implant interface by inhibiting osteoclastic activity (Yaffe et al. 1995, 1997, 1999)
- a positive correlation between increased bone density and higher implant mechanical properties (Peter et al. 2005).
BUT
BRONJ
BRONJ Definition

- Exposed bone
- Maxillofacial region
- > 8 weeks
- BP exposure
- No history of radiation therapy to craniofacial region

Khosla S et al 2007
Khan et al 2008
Rizzoli 2008
AAOM 2009
BRONJ – Presenting features

- Exposed bone
- Pain
- Infection +/-extraoral/intraoral fistula
- Traumatic ulceration 2$^0$ to sharp exposed bone
- Halitosis
- Paraesthesia
- Fractured mandible
## Staging & management of BRONJ

Adapted from AAOMFS position paper 2007; Migliorati 2005; Ruggiero 2006

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Risk</td>
<td>No exposed bone</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic exposed bone</td>
</tr>
<tr>
<td>2</td>
<td>Exposed bone + pain +/- infection</td>
</tr>
<tr>
<td>3</td>
<td>Exposed bone + pain + infection +/- fracture +/− E/O fistula</td>
</tr>
</tbody>
</table>
## Classification of BRONJ

Adapted from Madrid et al 2007

<table>
<thead>
<tr>
<th>Disable ONJ</th>
<th>Non-disabling ONJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate – Severe pain (VAS 3-10)</td>
<td>Absent or controlled pain (VAS ≤ 3)</td>
</tr>
<tr>
<td>Diffuse infection</td>
<td>Infection absent or controlled</td>
</tr>
<tr>
<td>Mastication impossible</td>
<td>Mastication satisfactory</td>
</tr>
<tr>
<td>Social life severely impaired</td>
<td>Acceptable social life</td>
</tr>
</tbody>
</table>
PCP acts as bone hook
Essential for binding to HA

R² chain determines potency

PCP group essential for biological activity

If R¹ is an OH, group binding to HA is enhanced

Ann Pharmacother 2005, 39:668-677
Pharmacology of BPs

Presence or absence of NH2 → Osteoclastic effect

Non-NH2 BPs
clodronate & etidronate
antagonise cell ATP →
• cell apoptosis
• ↓ bone resorption

NH2 BPs
PA, AA, RA, ZA
Inhibit mevalonate pathway →
• Osteoclast apoptosis
• Loss of adherence of osteoclasts to bone surface

Zoledronic acid inhibits human endothelial cell proliferation & modulates endothelial cell adhesion & migration

Devogelaer 2000
Fleisch 2002
Woo 2006
Dass 2007
McLeod 2007
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Nitrogen-containing</th>
<th>Route of admin</th>
<th>Potency</th>
<th>FDA approval</th>
<th>Cases of BRONJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>Didronel</td>
<td>N</td>
<td>Oral</td>
<td>1</td>
<td>1977</td>
<td>None</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Bonefos</td>
<td>N</td>
<td>Oral</td>
<td>10</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>Skelid</td>
<td>N</td>
<td>Oral</td>
<td>10</td>
<td>1997</td>
<td>None</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Aredia</td>
<td>Y</td>
<td>IV</td>
<td>100</td>
<td>1991</td>
<td>211</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Fosamax</td>
<td>Y</td>
<td>Oral</td>
<td>100-1000</td>
<td>1995</td>
<td>63</td>
</tr>
<tr>
<td>Alendronate plus vitamin D</td>
<td>Fosamax plus D</td>
<td>Y</td>
<td>Oral</td>
<td>100-1000</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>Actonel</td>
<td>Y</td>
<td>Oral</td>
<td>1000-10000</td>
<td>1998</td>
<td>12</td>
</tr>
<tr>
<td>Risedronate plus calcium carbonate</td>
<td>Actonel with calcium</td>
<td>Y</td>
<td>Oral</td>
<td></td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Boniva</td>
<td>Y 3rd gen</td>
<td>Oral/IV</td>
<td>1000-10000</td>
<td>2003</td>
<td>2</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Zometa</td>
<td>Y</td>
<td>IV</td>
<td>10000+</td>
<td>2001</td>
<td>219</td>
</tr>
<tr>
<td></td>
<td>Aclasta</td>
<td>Y</td>
<td>IV</td>
<td>10000+</td>
<td>2008</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Zahrowski 2007; Hess 2008; Sarin 2008 Black 2008
Pharmacology – drug elimination

<table>
<thead>
<tr>
<th>Elimination phase</th>
<th>Where</th>
<th>Drug</th>
<th>Total elimination time</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (hours)</td>
<td>50% through kidneys</td>
<td>Ibandronate</td>
<td>37-157 hrs</td>
</tr>
<tr>
<td>II (weeks)</td>
<td>Drug leaves high bone turnover areas</td>
<td>Zoledronate</td>
<td>146 hrs</td>
</tr>
<tr>
<td>III (years)</td>
<td>Sequestered drug leaving from slow bone turnover areas</td>
<td>Risedronate, Pamidronate, Alendronate</td>
<td>224-480 hrs, 300 days, 10 years</td>
</tr>
</tbody>
</table>

Zahrowski 2007
Epidemiology
### BRONJ Incidence – 2008 studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Oral/I V</th>
<th>Incidence</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boonyapakorn 2008</td>
<td>80</td>
<td>IV</td>
<td>28% : MM+ breast CA + other CA</td>
<td>Prospective</td>
</tr>
<tr>
<td>Hoff 2008</td>
<td>4019</td>
<td>IV</td>
<td>1.2% breast cancer 2.4% MM</td>
<td>Retrospective</td>
</tr>
<tr>
<td>La Verde 2008</td>
<td>186</td>
<td>IV</td>
<td>8.6%</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Rizzoli 2008</td>
<td>443</td>
<td>Oral</td>
<td>54 cases 1 per 100,000 person-years exposure</td>
<td>Review of literature</td>
</tr>
<tr>
<td>Walter 2008</td>
<td>43</td>
<td>IV</td>
<td>18.6% Prostate CA cohort</td>
<td>Prospective X-sect</td>
</tr>
<tr>
<td>Estilo 2008</td>
<td>310</td>
<td>IV</td>
<td>95</td>
<td>Retrospective</td>
</tr>
<tr>
<td>King 2008</td>
<td>481</td>
<td>Oral/I V</td>
<td>94.2% cases IV 5.8% cases oral</td>
<td>Review of literature</td>
</tr>
</tbody>
</table>
BRONJ Incidence

Higher numbers reported by:
- Council on Scientific Affairs of the ADA
  - 170 cases to alendronate
- Medical claims databases

No RCTs or well-designed clinical trials testing efficacy or safety of BPs in osteoporosis/Pagets report ONJ cases

Black 2007; Pazianas 2007; Gueiros 2008; Reid 2008; Edwards 2008
Risk factors:

Drug-related
Local
Demographic
<table>
<thead>
<tr>
<th>Drug-related</th>
<th>Local</th>
<th>Systemic &amp; demographic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose/Potency</strong></td>
<td>Surgical procedures</td>
<td>Age 78% &gt;60yrs</td>
</tr>
<tr>
<td>ZA &gt; PM</td>
<td>- exts in up to 80%</td>
<td>Gender F&gt;M for oral</td>
</tr>
<tr>
<td>PM &gt; oral BPs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Anatomy</td>
<td>Race</td>
</tr>
<tr>
<td>IV &gt; oral</td>
<td>- Mandible &gt; maxilla</td>
<td>- Caucasians</td>
</tr>
<tr>
<td></td>
<td>- Areas of thin mucosa</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Concomitant oral disease</td>
<td>Cancer diagnosis</td>
</tr>
<tr>
<td>ZA from 1% - 21% at 3yrs</td>
<td>Trauma</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Oral BPs &gt; 3 yrs</td>
<td>Dentures</td>
<td>DM/RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative risk</strong></td>
<td></td>
<td>Smoking/alcohol</td>
</tr>
<tr>
<td>&gt;1% at 1yr</td>
<td></td>
<td>Corticosteroid use</td>
</tr>
<tr>
<td>11% at 4yrs</td>
<td></td>
<td>Immunosuppressant use</td>
</tr>
</tbody>
</table>

Pathogenesis
<table>
<thead>
<tr>
<th>Theories</th>
<th>Pathogenic basis</th>
<th>Refs</th>
</tr>
</thead>
</table>
| 'Inside-out'  | BP-induced low bone turnover  
   ↓ Osteoblast cell viability as BP conc ↑  
   Bone cell necrosis & apoptosis  
   Exposed non-healing bone areas  
   ↓ Blood flow  
   Infection                                                                                         | Ruggiero 2004; Bauss 2008; Yarom 2007; Naidu 2008 |
| 'Outside-in'  | Mucosal damage then infection & subsequent bone necrosis                                                                                                                                                             | Hoff 2005; Landesberg 2008; Reid 2008 |
| Angiogenesis inhibition | Mediated through inhibition of VEGF  
   (↓ levels shown in vitro & in vivo)  
   & other angiogenic factors.  
   BPs cause ↓IL-17 a proangiogenic cytokine  
   ↓endothelial cell proliferation, adhesion & migration in rats  
   Obliteration of vessels in <30%                                                                 | Wood 2002; Croucher 2003; Vincenti 2005; Oteri 2008; Hansen 2007 |
| Direct mucosal effect | High local BP concentration  
   Toxic to oral epithelium at pharmacological concentrations                                                                                              | Reid 2007; Diel 2007; Marx 2008 |
| Multifactorial | Immunosuppressed/medications/smoking/age/wound healing                                                                                                                                                             | Rizzoli 2008                   |
| Infection Interleukins | Microbial biofilms - actinomyces  
   Improvement with antibiotics  
   ?Role of effect of bacteria on IL6 production in osteoblasts  
   Direct effect of BPs on cells of immune system                                                                                          | Khosla 2007; Reid 2008; Sedghizadeh 2008 |
Microtrauma → teeth, forces of mastication & daily function or local infection/ext → Microfractures in acellular, avascular bone. Suppression of bone remodelling → poor repair

Bone turnover 10-100x > in jaws than long bones

High vascularity with high bone turnover → ↑ concentration of BPs

Bone turnover

 role of bacteria

 keratinocyte cell cycle inhibition & effect on wound healing

 BP concentration in gingival crevicular fluid similar to bone

Mucosal damage can be caused by oral BPs

BPs in bone at dose high enough to be directly toxic to oral epithelium – inhibit keratinocyte cell cycle hindering repair mechanisms

Thin mucosa traumatised & contact with causative bacteria actinomyces, eikenella for caries & perio disease

Why Jaw Bones?
Suggested Hypotheses

Migliorati 2006; Sarin 2008; Allen 2008; Bauss 2008; Landesberg 2008; Reid 2008
Oral BPs
Osteoporosis in 12 million >50 yrs & osteopenia in 40 million >50 yrs by 2010 in US
- ↓ risk of vertebral fractures by 40-50% & non-vertebral fractures by 20-40%
- >190 million prescriptions for oral BPs worldwide
- Relative prevalence ONJ low
- Oral BPs responsible for <5% of all cases ONJ
- Majority → alendronate
- Mean time to ONJ 4.1yrs
- Oral & IV formulations of ibandronate for osteoporosis

Zahrowski 2007; Yarom et al 2007; Macleod 2007; Migliorati 2008; Edwards 2008
<table>
<thead>
<tr>
<th>Image modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **OPT**        | Inexpensive
                Widely available
                Osteolysis & osteosclerosis
                Use as 1st line | Less useful if osteolytic
                Difficult to demarcate margins between necrotic & healthy bone
                Early lesions often missed |
| **CT**         | 3D image
                Differential diagnosis & extent
                Cortical involvement | No additional info in asymptomatic patient with ON |
| **Cone beam CT** | Lower radiation dose
                    Higher spatial resolution than CT
                    Better image quality
                    Cortical integrity, marrow & cancellous BMD | Limited in discrimination of soft tissues
                    Low contrast resolution
                    Not yet widely available |
| **MRI**        | With contrast gadolinium region of ischaemia recognised
                Soft tissue extension | Data limited
                May be associated with ++ false positives |
<table>
<thead>
<tr>
<th>Image modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99 radioisotope scintigraphy</td>
<td>Screening Subclinical lesions</td>
<td>Assumes change in vascularity within necrotic region High radiation exposure Lengthy procedure</td>
</tr>
<tr>
<td>PET</td>
<td>Functional test [\uparrow] uptake in areas of ONJ</td>
<td>Poor resolution High radiation dose</td>
</tr>
<tr>
<td>Optical coherence tomography</td>
<td>No ionizing radiation Image small pre-lesions in alveolar bone</td>
<td>Depth of penetration image artifacts</td>
</tr>
<tr>
<td>Sequential images</td>
<td>Provide temporal history of developing change</td>
<td></td>
</tr>
</tbody>
</table>
BRONJ – Further Investigations

**Biopsy** → to rule out metastatic disease in high risk patients

**Histopathology**
- Chronic inflammatory infiltrate
- Empty & osteocyte-occupied lacunae
- Necrotic bone usually surrounded by colonies of microbes

**Microbial culture**
- Actinomyces, lactobacillus, candida
- Identification of pathogens → 2⁰ infections

**Suggested:**

**C-terminal telopeptide**

Bone turnover marker *(Marx 2007)*

*Carter 2005; Dannemann 2006; Kim 2007; Yarom et al 2007; Chiandussi et al 2007; Bedogni 2007; Oda and Bagan 2008; Lobato 2008*
No scientific data to support use of CTX to predict development of BRONJ

Validation in clinical trials needed

Expect low CTX if taking BPs as ↓ bone resorption

↓ CTX to <150pg/ml a surrogate index of drug efficacy

To stop BP based on CTX risks losing BP effect & ↑ risk of fractures

CTX not a gold standard for BRONJ

Khosla ASBMR 2008; Edwards 2008
Baim and Miller 2009
Management
General Consensus

- INFORM PATIENTS OF RISK
- Consult physician
- Good OH
- Smoking cessation
- ↓Alcohol
- Pre-Tx dental assessment
- Extract unsalvageable teeth
- Complete all invasive dental procedures
- Aim to achieve optimal periodontal health
BRONJ – Prevention

Oral
- Routine dental care
- Regular radiographs
- Educate patient
- Informed consent for surgical procedures

IV for CA & OP
- Educate patient
- Evaluate dental/perio status
- Full mouth intraoral & panoramic radiographs
- Plaque control
- Restore carious teeth
- RCT for non-vital teeth
- Extract poor prognostic teeth prior to start of Tx
- Avoid surgery after start of Tx
- Routine dental care regularly

Dannemann 2006
Ruggiero 2008
Preventive measures are effective

- ↓ incidence BRONJ with implementation of dental preventive measures
- ↓ infection rates of any non-infected, already necrotic, exposed bone
- Retrospective & prospective studies
  - MM cases taking ZA
  - Cancer patients with bone metastases

AAOMFS 2007; Walter 2008
Dimopoulos 2008; Ripamonti 2008; La Verde 2008
Management guidelines

Since AAOM position paper 2005
- Consensus papers have been published & preservation of QoL through control of pain and infection defined
  - American Society Bone Mineral Research 2007
  - American Association OMFS 2007
  - Canadian Consensus practice Guidelines for BRONJ 2008
  - American Association of Oral Medicine 2009
BRONJ Management

Goal - to preserve QoL

- Control pain
- Manage infections
- Maintain function (speech & mastication)
- Prevent new areas of necrosis
- Social life (halitosis)
- Patient education
- Patient reassurance
- Support of continued oncological Tx

ASBMR 2007; AAOMFS 2007
Management of Bisphosphonate Related Osteonecrosis of the Jaw in Lausanne
## Prevention

<table>
<thead>
<tr>
<th>Patients referred before IV BP treatment</th>
<th>Multiple Myeloma M/F</th>
<th>Prostate Cancer M</th>
<th>Breast Cancer F</th>
<th>Severe Osteopenia F</th>
<th>Total M/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>11/10</td>
<td>5</td>
<td>4</td>
<td>-</td>
<td>16/14</td>
</tr>
<tr>
<td>2006</td>
<td>10/4</td>
<td>5</td>
<td>6</td>
<td>-</td>
<td>15/10</td>
</tr>
<tr>
<td>2007</td>
<td>9/3</td>
<td>7</td>
<td>11</td>
<td>-</td>
<td>16/14</td>
</tr>
<tr>
<td>2008</td>
<td>8/3</td>
<td>11</td>
<td>13</td>
<td>8</td>
<td>19/26</td>
</tr>
<tr>
<td>total</td>
<td>58</td>
<td>28</td>
<td>34</td>
<td>8</td>
<td>66/62</td>
</tr>
<tr>
<td>Total screened patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>128 patients 66/62</td>
</tr>
<tr>
<td>Patients referred before IV BP treatment</td>
<td>Multiple Myeloma</td>
<td>Prostate Cancer</td>
<td>Breast Cancer</td>
<td>Severe Osteopenia</td>
<td>Total</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Total extraction patients</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Partial extraction patients</td>
<td>32</td>
<td>21</td>
<td>12</td>
<td>3</td>
<td>68</td>
</tr>
<tr>
<td>Conservative treatment</td>
<td>21</td>
<td>19</td>
<td>11</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>Hospital</td>
<td>37</td>
<td>32</td>
<td>18</td>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>Private Dentist</td>
<td>20</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>
## Prevention

<table>
<thead>
<tr>
<th>Patients referred before IV BP treatment</th>
<th>Multiple Myeloma</th>
<th>Prostate Cancer</th>
<th>Breast Cancer</th>
<th>Severe Osteopenia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>58</td>
<td>28</td>
<td>34</td>
<td>8</td>
<td>66/62</td>
</tr>
<tr>
<td>BRONJ occurrence</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2/128</td>
</tr>
</tbody>
</table>

Mean Follow-up 18.4 months

1.56%
## TREATMENT BASED ON STAGING

(adapted from AAOMFS 2009)

<table>
<thead>
<tr>
<th>At risk</th>
<th>No treatment</th>
<th>Patient education</th>
</tr>
</thead>
<tbody>
<tr>
<td>(No bone exposed)</td>
<td>Remove sharp bone &amp; loose segments of bone</td>
<td>Patient education</td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td>Antimicrobial M/W – chlorhexidine 0.12%</td>
<td>Remove sharp bone &amp; loose segments of bone</td>
</tr>
<tr>
<td>Asymptomatic bone exposure</td>
<td>Regular follow-up</td>
<td>Antimicrobial M/W – chlorhexidine 0.12%</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>Broad-spectrum antibiotics</td>
<td>Regular follow-up</td>
</tr>
<tr>
<td>Bone exposed + infection</td>
<td>- Penicillin</td>
<td>Antibiotic M/W</td>
</tr>
<tr>
<td></td>
<td>- Doxycyclin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Metronidazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Cephalosporin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Superficial debridements</td>
<td>Antibiotic M/W</td>
</tr>
<tr>
<td></td>
<td>Antibiotic M/W</td>
<td></td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>Antibiotics</td>
<td>Extract symptomatic teeth in area of ON</td>
</tr>
<tr>
<td>Exposed bone + pain, infection,</td>
<td>Surgical debridement/resection</td>
<td>Antibiotic M/W</td>
</tr>
<tr>
<td>fracture/fistula</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Management

- Conservative management of non-disabling BRONJ

- Daily instillation of chlorhexidine 0.12% without alcool on bone exposition by patient or health professional

- Long course antibiotic therapy
  - Amoxicillin 2 to 3 g/d
  - Or:
    - Levofloxacin (Tavanic): 500mg /d
    - Doxycyclin (Vibramycine): 200mg /d
    - azithromycin (Zythromax): 250mg /d

- Professional dental hygiene every 3 months
Case report 1

- Female 58 y
- 7 y breast cancer evolution
- Multiple bone metastasis
- Pamidronate: 11 m
- Zoledronate: 10 m
- Dental treatment including extractions after 14 m
- BRONJ discovery after 21 m
- Non disabling
- Conservative management
M: 20
Case report 1

- Died of her cancer 28 months after discovery of BRONJ
- Still classified non disabling BRONJ 2 months before death
Management

- Non-Conservative management of disabling BRONJ
  - Long course antibiotic therapy
    - Amoxicillin 3 g/d
    - Or:
      - Doxycyclin (Vibramycin): 200mg /d
      - Levofloxacin (Tavanic): 500mg /d
      - Azithromycin (Zythromax): 250mg /d
  - Professional dental hygiene every 3 months
  - Surgery limited to elimination of necrotic bone and infection control
  - Exposition coverage by local flaps
Case report 2

- 64 yr old female 72 kg
- PMH - nil of note
- Developed headache & chest pain Feb 07
- Afebrile
- ESR: 100 mm/h  CRP:12 mm/l
- March 2007 - superficial temporal artery biopsy
- - suggestive of diffuse Giant Cell Arteritis
- 60 mg Prednisone & Azathioprine 150mg
- May 2007: ESR 35  CRP 10
- Prednisone ↓ 20mg/day
- September 2007
- Fall in her garden
- Asymptomatic fracture of L1 vertebra
- GMP → osteopenia $2^0$ to Prednisone
- Oral Ibandronate 150 mg/month for 6mths
Oct/Nov 07 – 2 doses Ibandronate 150mg
- 14.12.07: pain left lower jaw
- GDP - mouth ulcer & abcess
- LL6 ridge
- LL6 extracted 6 yrs previously
- Wearing -/P for the last 15 yrs
- 24\(^{th}\) Dec 07 – skin fistula L suprahyoid
- Her GMP
  - Stopped Ibandronate after 2 doses
  - Systemic antibiotics Dec 07 – Feb 08
- Symptoms improve

- No resolution
- Patient referred to Oral Medicine
- ? osteonecrosis of the jaw
- 19/03/08 - 1st examination Oral Med
- Levofloxacin 500 mg/day
- Oral Metronidazole 1.5 g/day
Clinical Examination

Bone exposure LL6 ridge

Pus from cutaneous fistula
27.03.2008
Curettage of bony sequester

Panoral radiograph depicts proximity to ID canal
27.03.2008
Curettage of bony sequester
27.03.2008
Curettage of bony sequestrum
Postoperative

First intention healing →
30 days after surgery
- Amoxicillin 3g/day
- Metronidazole 1.5g/day
- No denture wearing
Follow-up May 2009
AB stopped in November 2008
Management

- Non-Conservative management of disabling BRONJ

- Long course antibiotic therapy
  - Amoxicillin 3 g/d
  - Or:
    - Doxycyclin (Vibramycin): 200mg/d
    - Levofloxacin (Tavanic): 500mg/d
    - azithromycin (Zythromax): 250mg/d

- Professional dental hygiene every 3 months

- Large surgery to eliminate large portions of necrotic bone and control regional infection

- Exposition coverage by local flaps
Case report 3

- Female 47 y
- Portugal
- Referred by ENT for « assessment »
- Breast cancer diagnosed in 2000
- Bone metastasis May 2004
- Tooth extractions by her dentist in February 2007 in the left maxilla
- New tooth extractions in April 2007
- Referred by dentist to ENT for sinusitis June 2007
- June 2007- September 2007 several surgical treatments of sinusitis
- September 2007 decides to come to Lausanne
December 2007

Surgical elimination of all necrotic bone and sinusal revision by Caldwell-Luc approach

Vestibular flap to close oro-antral fistula

Controlled every two months until December 2008.

- No re-opening
- No recurrence of osteomyelitis
- On ciprofloxacin since September 2007 developed peripheral paresthesia in June 2008
Lausanne flow-chart

Disabling BRONJ

Non conservative management

Debridment surgery
Sequestrectomy
Fracture contention

Non desabling BRONJ

Conservative management

Conservative management

Minimally invasive BRONJ surgery

Full healing
Management update – surgery

- 70-82% success rate with surgery & low level laser therapy (Nd:YAG laser)  
  - Vescovi 2008

- Significant improvement between preop & postop staging with minimal resection of necrotic bone + local soft tissue closure  
  - Wutzl 2008

- Case reports of radical surgery application  
  - Yarom 2007; Abu-Id 2007; Nocini 2008; Engroff 2008
Insufficient evidence to recommend

Marx 2003; Ruggiero 2004; Migliorati 2005; Shimura 2006; Marunick 2006; Freiberger 2007; Van Den Wyngaert 2007
BRONJ – Other reported treatment options

- Laser therapy
- Platelet-derived growth factor
- Platelet-rich plasma
- Ozone therapy combined with surgery & antibiotics
- Slow extraction with orthodontic bands
- Systemic teriparatide

Drug holiday
BP Drug holiday

- Counteract antiangiogenic effects of BPs
- Allow improvements in soft tissues & periosteum
- If discontinued for 4 half lives (approx 1-2 months) > 90% of drug clearance from high bone turnover areas

Suggested that patients taking oral BPs could have a drug holiday of 3-6 months before elective alveolar surgeries.

- No prospective data
- Evaluated on a case by case & risk/benefit basis
- No reports that support or oppose the discontinuation of BPs given iv once ONJ develops
- No scientific evidence to support the idea that discontinuing BP therapy will improve Tx outcomes
- Much could be lost in pathology for which drug originally prescribed - for little gain

Other BP dosing regimes

3 year RCT of ZA versus placebo
- >7000 post-menopausal women with osteoporosis
- Yearly admin 5mg IV ZA associated with 1 case ONJ (same frequency as placebo)

2 year retrospective study
- 3 monthly ZA for MM ↓ risk of ONJ while maintaining anti-resorptive effect of drug

Black 2007; Corso 2008
Consultation with oncologist
Complete necessary dental Tx before start
Non-urgent surgical Tx while on BPs consider stopping BPs for 3-6 mths pre-op & until surgical site healed
If Tx urgent proceed & consider BP cessation during healing period
Symptomatic teeth located within area of bone already exposed & necrotic - extraction should be considered because it is unlikely that it will exacerbate the established necrotic process

Symptomatic teeth that would otherwise require extraction should receive nonsurgical endo or perio Tx and left in situ
Avoid implants
Dental evaluation pre-Tx & continued 6-12 mthly
Oral BPs - dental management

Prevention

Before BP Tx
- Inform all patients
- Dental assessment
- Routine dental care
- Treat active oral infections & ↓ risk of further infections
- Allow time for epithelial healing post-surgery

Taking BPs
- Conservative dental Tx
- Interrupt BP in case of dental surgery → decision on a case by case basis

Treatment

BRONJ diagnosed
- Conservative management where possible
- Remove necrotic bone with minimal trauma to adjacent hard and soft tissue
- Topical antibiotic M/W
- ABx therapy
- Avoid extensive oral surgical procedures

Adapted from AAOMFS 2007;
Canadian Consensus 2008; Rizzoli 2008
All pts undergoing implant placement:
- Which drug?
- Dose?
- Duration prior to surgery?

Oral BP >3 yrs & taking prednisolone
- Alternative Tx options

Bell 2008; Graham 2008
prospective and retrospectives studies about safety of implant placement in patients treated by oral-BPs

---

**Madrid and Sanz, 2009**

<table>
<thead>
<tr>
<th>Study/ Year</th>
<th>Number of patients Test/control</th>
<th>Age range. (years)</th>
<th>Bisphosphonate/ Dosage</th>
<th>BP intake duration at implant placement</th>
<th>Number of implants Test/control</th>
<th>Follow-up duration (months)</th>
<th>BRONJ Number</th>
<th>Success rate in BP group</th>
<th>Success rate in control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffcoat MK 2006</td>
<td>25/25</td>
<td>?</td>
<td>Alendronate Risedronate</td>
<td>1 to 4 y</td>
<td>102/108</td>
<td>36</td>
<td>0</td>
<td>100%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Fugazotto PA 2007 retrospective analysis</td>
<td>61/ no control</td>
<td>51 to 83</td>
<td>Alendronate (52 patients) 70 mg/week (30) 35mg/week (22) Risedronate (9 patients) 35 mg/week (6) 70mg/week(3)</td>
<td>1.25 patients 4 to 5 years 2.36 3 years and less mean : 3.3 y</td>
<td>169/no control</td>
<td>12 to 24</td>
<td>0 (1 case of bone exposition not matching BRONJ criteria)</td>
<td>100%</td>
<td>No control group</td>
</tr>
<tr>
<td>Bell BM and Bell RE 2008 retrospective analysis</td>
<td>42/not communicated</td>
<td>Not communicated</td>
<td>Alendronate (34 patients) risedronate (6 patients) ibandronate (2 patients) doses :not communicated</td>
<td>Not communicated</td>
<td>100/734</td>
<td>4 to 89 average 37</td>
<td>0</td>
<td>95%</td>
<td>96.5%</td>
</tr>
<tr>
<td>Grant BT 2008 retrospective analysis</td>
<td>89 patients under BP before implant surgery/1319 female patients with implant surgery</td>
<td>Mean :67.4</td>
<td>Alendronate (66 patients) Risedronate (21 patients) Ibandronate (2 patients)</td>
<td>38 months</td>
<td>468/1450</td>
<td>48</td>
<td>0</td>
<td>99.5%</td>
<td>99%</td>
</tr>
</tbody>
</table>
Guidelines on implant therapy in cancer and osteoporotic patients taking IV or oral BPs

<table>
<thead>
<tr>
<th>Guidelines author</th>
<th>Association or Task Force</th>
<th>Implant placement in cancer patient</th>
<th>Implant placement in oral-BP patient</th>
<th>Antibiotic prophylaxis</th>
<th>Discontinuation of bisphosphonate before/after placement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migliorati CA 2006</td>
<td>American Academy of Oral Medicine</td>
<td>No position</td>
<td>No position</td>
<td>Not addressed</td>
<td>No position</td>
</tr>
<tr>
<td>No author listed 2007</td>
<td>French Agency for Safety of Health Products</td>
<td>contraindicated</td>
<td>No contraindicated</td>
<td>Not addressed</td>
<td>No position</td>
</tr>
<tr>
<td>No author listed 2007</td>
<td>American Dental Association Council on Scientific Affairs</td>
<td>Not addressed</td>
<td>- Should be considered carefully - extensive implant placement or GBR at risk</td>
<td>Not recommended To be considered: In risky patients for risky procedures</td>
<td>Not addressed</td>
</tr>
<tr>
<td>No author listed 2007</td>
<td>American Association of Oral and Maxillofacial surgeons</td>
<td>Should be avoided</td>
<td>-BP intake &lt;3 y: no contraindication -BP intake &gt;3 y or &lt;3y+corticosteroids: drug holiday recommended</td>
<td>Not addressed</td>
<td>Oral-BPs: 3 month before 3 months after</td>
</tr>
<tr>
<td>Khosla S 2007</td>
<td>American Society of Bone and Mineral Research</td>
<td>Not recommended</td>
<td>Not contraindicated</td>
<td>Not addressed</td>
<td>-no data to suggest improvement of outcomes -discontinuation of oral-BP unlikely to have adverse effect</td>
</tr>
<tr>
<td>Edward BJ 2008</td>
<td>American Dental Association Council on Scientific Affairs</td>
<td>Not addressed</td>
<td>-Dentists should consider treatment options -extensive implant placement or GBR at risk -non surgical therapy of peri-implantitis</td>
<td>No evidence that antibiotics prevent BRONJ</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Khan AA 2008</td>
<td>Canadian Consensus Practice for BPs associated osteonecrosis of the Jaw</td>
<td>Not recommended</td>
<td>Currently not contraindicated</td>
<td>Not addressed</td>
<td>-to be considered in case of non-emergent invasive dental procedure: 3 to 6 months before procedure and until healing is achieved</td>
</tr>
</tbody>
</table>
Alternatives to bisphosphonates or dosing regimes

**PROSTATE CANCER**
- Endothelin receptor antagonists
- Calcitriol
- PSMA antibody
- Proteasome inhibitors
- Thalidomide
- Growth factor receptor inhibitors

**MULTIPLE MYELOMA**
- Thalidomide
- Lenalidomide
- Bortezomib
  - (3mthly versus 1 mthly infusions of ZA to ↓ incidence of BRONJ)

**OSTEOPOROSIS & BONE DISEASES**
- Denosumab
- ERT HRT SERM
- Aromatase inhibitors
- ERD
- Calcitonin
- PTH
- Strontium ranelate

**CHANGES IN BP DOSING SCHEDULES**
- Published guidelines for Osteoporosis & MM
- Yearly IV Zolendronate for osteoporosis

**PAGET’S DISEASE**
- Recombinant osteoprotegerin

---

**No ZA for early MM**
- Discontinue after 2 yrs

---

Smith 2005; Cundy 2005; Capsoni et al 2006; Lacy et al 2006; Corso 2007; Johnson 2007; Reginster 2008
Conclusions

- Important area of vigilance for GDPs, physicians, Oral Medicine & Oral Surgeons
- Minimally invasive surgery
- Collaboration
  - oncologists and oral surgeons
  - bone disease specialists and oral surgeons
Acknowledgements

- Prof Bertrand Jaques and Doctor Martin Broome Division de Chirurgie Maxillo-Faciale CHUV Lausanne
- Doctor Ann Hegarty Eastman Institute for Oral Health Care London
- Doctor Kahina Bouferrache and Doctor Marcelo Abarca Service de Stomatologie et Médecine Dentaire Policlinique Médicale Universitaire Lausanne