Bisphosphonate-induced Jaw Osteonecrosis (BJON) & its Management Strategy

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Abstract

Bisphosphonates administered intravenously are used to treat patients with cancer who have hypercalcemia associated with malignant disease, multiple myeloma or metastatic tumors (breast, lung, prostate) in the bones. Bisphosphonates are bone resorption inhibitors and have been associated with osteonecrosis of the jaws. Osteonecrosis of the jaws is a major complication associated with long-term use of bisphosphonates. While osteonecrosis can arise from other precipitating conditions, bisphosphonate-induced jaw osteonecrosis (BJON) is highly associated with long-term administration of pamidronate and zoledronic acid, which are two intravenous bisphosphonate formulations. The underlying pathogenesis of BJON and its site-specific presentation still remain to be fully elucidated. Some clinical recommendations on prevention and management are suggested, as summarized from current literature.

Introduction

The exposure of necrotic maxillary or mandibular bone in patients treated with bisphosphonates is becoming increasingly questionable. Bisphosphonates[1] (Table 1) are non-metabolizable pyrophosphate analogs, with a preference for bone tissue. They act on osteoclasts (through a membrane receptor or an intracellular enzyme),[2] inhibiting chemotaxis, shortening their average life span, halting their activity and inducing apoptosis.[3] As a result, bone resorption is stopped. Zoledronate and pamidronate also inhibit capillary neoangiogenesis of the tumor.[4-6]

Generally,[7] bisphosphonates are indicated for stabilizing the loss of bone mass in postmenopausal women with osteoporosis (and they are taken orally). Intravenous administration is reserved for cases of bone metastases (principally breast and prostate) and for correcting bone resorption, or moderate-to-severe hypercalcemia in cases of multiple myeloma. It is also recommended for osteolytic lesions caused by any type of solid tumor.[2, 8] In 2003 Marx[7] published a series of 36 maxillary or mandibular exposure cases due to bisphosphonates. From then on numerous cases have been reported, and many more are to be expected given the wide use of these drugs among the population.

The initial phase of the disease[2, 9] typically starts with post-extraction alveolitis (although there are spontaneous cases) refractory to treatment, which progresses towards osteomyelitis, with sequestrum, bone exposure, inflammation and suppuration. Biopsies are frequently carried out in order to rule out mandibular bone metastases or primary jaw bone tumors. Failure occurs when trying to cover these areas even though meticulous regularization or bone resection has been carried out together with closure with local mucosal flaps. Clinically and radiologically the lesions are like those from osteoradionecrosis with sequestrum (that form spontaneously or after invasive procedures) that can complicate due to secondary infections.[2]

Its pathogenesis lies in the interruption of osteoclastic remodeling activity and from bone cell turnover,[7] which is aggravated by localized vascular insufficiency as a result of ischemic changes.[2] This inhibition is partial in the case of oral bisphosphonates, as osteonecrosis rarely arises and only following high accumulated doses over long periods of time. If administered intravenously, osteoclastic inhibition is irreversible, and apoptosis will take place.[7] This is a characteristic entity of the jaw bones. These drugs have a preference for them given their profuse vascular supply and the high cellular turnover (there is great bone remodeling activity around the periodontal ligament). Other factors include the limited thickness of the mandibular-maxillary mucosa and the frequent “aggressive behavior” suffered by the bone in the way of invasive surgical or dental procedures. It predominates in the upper jaw (38-80.5%); while 14-63% is located in the mandible and 5.5-23% in both.[2, 10]

Clinical recommendations for prevention and management

Prevention is always better than cure, and this also applies to BJON.[11, 12] Clinicians should encourage regular dental checks. If possible, patients about to begin bisphosphonate therapy should have a dental examination before or soon after initiating therapy.
Elimination of all potential sites of infection must be the primary objective of the consultation. The importance of good dental hygiene should be emphasized, and patients should be made fully aware of the benefits and risks so that they can make an informed decision about whether they should start treatment.

Some health care professionals recommend stopping bisphosphonates for several weeks before and after dentoalveolar surgery. Given the long half-life of bisphosphonates in bone (up to 12 years), it is unlikely that this practice would have an adverse impact on the therapy of osteoporosis or Paget disease. However, it is also unclear whether such practice would have any effect to reduce the risk of developing BJON.

Teeth with extensive caries should be considered for endodontic therapy. They should be prepared as overdenture abutments. The crown should be excised at the gingival margin. This is especially important in patients with a history of extractions that resulted in BJON. In these patients, extraction should be avoided. If extraction has to be performed, the following should be taken into consideration[13]:

1. Document the reason for extraction (written/radiographic).
2. Provide the patient with balanced information about the risks and benefits of extraction and obtain informed consent.
3. Before extraction, minimize local infection and plaque accumulation by prophylaxis and chlorhexidine mouthrinses.
4. Avoid dental extractions if possible unless the teeth have a mobility score of 3 or greater. Extractions should be performed asatraumatically as possible. Patients should be followed up weekly for the first 4 weeks afterward and then monthly until the sockets are completely closed and healed. If there is an indication for antibiotic use (due to secondary infection), amoxicillin (alone or in combination with clindamycin) may help to reduce the incidence of local infection.
5. Remove grossly infected teeth as required. Periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis, and active abscesses are risk indicators and may cause BJON by themselves and should be dealt with appropriately. BJON may already be present, and extractions simply make it apparent.
6. If multiple teeth need extraction, remove one tooth, wait 2 months to allow healing, and if no problems arise, proceed cautiously with other extractions.
7. Prescribe peri-/postextraction antibiotics for significant infection or other clinical indicator.
8. Use postextraction chlorhexidine mouthrinses until healing is complete.

If there is any doubt, patients should be referred for specialist opinions, so that chronic periodontal problems and foreseeable dental extractions can be considered before treatment is started.

Management of BJON

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has suggested staging and treatment strategies for established cases of BJON (Table 2). Proper staging of the disease helps surgeons to decide whether surgical intervention is indicated and what the degree of surgical intervention should be.

Sometimes, a conservative approach is adopted if the patient is asymptomatic, except for irritation of adjacent soft tissues by exposed necrotic bone. The condition is treated according to stage 1 category, although surgical debridement with HBO therapy can also be planned. The employment of HBO before and after surgical debridement or even extractions in cases of established BJON follows recommendations proposed by Marx[7, 14] However, although there is relatively strong evidence in the literature to support the use of HBO in the management of osteoradionecrosis, the place of HBO in the prevention or treatment of BJON is as yet unclear.

Hyperbaric oxygen therapy is not without its disadvantages. It is expensive and timeconsuming. Furthermore, not every patient is fit for HBO therapy. Before commencement of the therapy, the following evaluations should be performed:

1. Chest radiograph to see whether there are any bullae, fibrosis, or pneumothorax
2. Lung function test including FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity), and the FEV1/FVC ratio.
3. An assessment of eustachian tube function to see whether the patient could clear the ears in descent to 14 m and whether prophylactic myringotomy and grommet insertion are indicated.

Conclusion

Bisphosphonates are useful for a number of medical conditions but are responsible for the emergence of BJON. Doctors and dental clinicians should be aware of this significant complication that can occur spontaneously or after any dentoalveolar procedure in the population at risk. Furthermore, dental professionals are in a unique position to identify and
diagnose this disease process early in its course. From a medicolegal point of view, patients receiving bisphosphonates should be informed of the possible risks associated before commencement of therapy. Dental practitioners should make a thorough medical history and take appropriate measures to prevent the occurrence of the difficult-to-manage BJON condition. Early referral to specialists should be made once BJON is suspected. Because research in this area is ongoing, health care workers are encouraged to monitor developments and should be prepared to modify their practice as new evidence becomes available. \[15\]

References

12. Landis BN, Richter M, Dojinovic I, Hugentobler M. Osteonecrosis of the jaw after treatment with bisphosphonates is irreversible, so the focus must be on prevention. BMJ 2006;333:982–983.
13. Hellstein JW, Marek CL. Bisphosphonate-induced osteochemonecrosis of the jaws: A ounce of prevention may be worth a pound of cure. Spec Care Dentist 2006;26:8–12.
Table 1: Examples of commercially available Bisphosphonates

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Primary Indication</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>Didronel</td>
<td>Proctor &amp; Gamble</td>
<td>Paget Disease</td>
<td>Oral</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>Skelid</td>
<td>Sanofi-Aventis</td>
<td>Paget Disease</td>
<td>Oral</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Fosamax</td>
<td>Proctor &amp; Gamble</td>
<td>Osteoporosis</td>
<td>Oral</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Actonel</td>
<td></td>
<td>Osteoporosis</td>
<td>Oral</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Aredia</td>
<td>Novartis</td>
<td>Bone metastases</td>
<td>IV</td>
</tr>
<tr>
<td>Zolendronate</td>
<td>Zometa</td>
<td>Novartis</td>
<td>Bone metastases</td>
<td>IV</td>
</tr>
<tr>
<td>(IV) Intravenous</td>
<td></td>
<td></td>
<td></td>
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</table>
### Table 2: Stages and treatment strategies for BJON as proposed by the AAOMS

<table>
<thead>
<tr>
<th>BJON staging</th>
<th>Treatment strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 Exposed/necrotic bone that is asymptomatic</td>
<td>• Antibacterial mouthrinse &lt;br&gt;• Clinical follow-up on a quarterly basis &lt;br&gt;• Patient education and review of indications for continued bisphosphonate therapy</td>
</tr>
<tr>
<td>Stage 2 Exposed/necrotic bone associated with pain and infection</td>
<td>• Symptomatic treatment with broad-spectrum oral antibiotics based on culture and sensitivity data &lt;br&gt;• Oral antibacterial mouthrinse &lt;br&gt;• Pain control &lt;br&gt;• Only superficial debridement to relieve tissue irritation</td>
</tr>
<tr>
<td>Stage 3 Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border</td>
<td>• Antibacterial mouthrinse &lt;br&gt;• Antibiotic therapy and pain control &lt;br&gt;• Surgical debridement/resection for longer term palliation of infection and pain</td>
</tr>
</tbody>
</table>
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