Thalassaemia: the dental implications of bisphosphonate therapy

Navdeep Kumar

Eastman Dental Hospital, London, UK

Abstract

Bisphosphonates (BP) are commonly used in individuals with thalassaemia to stabilise bone remodelling. However, in recent years, evidence has emerged that bisphosphonate related osteonecrosis of the jaw (BONJ) may occur. Cases of BONJ have recently been confirmed in individuals with thalassaemia. The pathogenesis is unclear with limited experimental evidence suggesting factors such as excessive reduction of bone turnover, impaired angiogenesis, infection and toxicity to soft tissues may contribute.2

The evidence base in relation to the presentation of BONJ, its management and risk reduction is limited. This review provides a summary of the information that is currently available.

Introduction

Bisphosphonates (BP) are commonly used in individuals with thalassaemia to stabilise bone remodelling. However, in recent years, evidence has emerged that bisphosphonate related osteonecrosis of the jaw (BONJ) may occur. Cases of BONJ have recently been confirmed in individuals with thalassaemia.1 The pathogenesis is unclear with limited experimental evidence suggesting factors such as excessive reduction of bone turnover, impaired angiogenesis, infection and toxicity to soft tissues may contribute.2

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Prevalence if BONJ

The true prevalence of BONJ remains uncertain as the data is controversial and inconsistent due to variability in the definition / diagnostic criteria.2 However it is apparent that the incidence of BONJ is higher in relation to the use of higher potency intravenous BPs, ranging between 2% and 28%, with the majority of studies suggesting an incidence of 5-8% (<1%).2,3 Incidence is time-dependent and dose-dependent, with the time to onset ranging from 4 to 120 months. The incidence of BONJ associated with oral BP is lower and is generally accepted to be less than 1% (0.01-0.34%).2,3 Incidence is again time-dependent and dose-dependent, with the time to onset ranging from 3 to 10 years.

A number of dental risk factors have been identified, including dental extraction (or other surgery to the jawbones) and dental/periodontal infection or mucosal trauma (dentures).4 It is important to note that in some cases, the invasive dental procedure may have been performed as a consequence of clinical features (e.g. pain) caused by pre-existing undiagnosed BONJ rather than being a precipitating factor. In these cases, dental extraction would have exposed bone that was already necrotic, leading to secondary infection, further painful symptoms, and finally a diagnosis of BONJ. Hence the incidence of spontaneous BONJ is probably higher than previously reported and may approach 50% of all BONJ cases.

BONJ is more often reported in the mandible rather than the maxilla as the latter is more vascular. Other factors which may contribute to a higher risk of BONJ include age, corticosteroid therapy, chemotherapy, anti-angiogenic drugs (bevacizumab and sunitinib), diabetes, smoking and genetic factors.

Levels of serum-based bone turnover biochemical markers of bone remodeling, such as C-terminal telopeptide (CTX) have been proposed as an objective means of predicting the risk of developing BONJ but the supporting evidence is not clear.5,6

Presentation

Diagnosis is largely clinical although imaging can support the diagnosis. BONJ classically presents with a 6-8 week history of transmucosal / trans-cutaneous exposure of necrotic bone often triggered by surgical trauma such as dental extractions. There is no history of previous radiotherapy to the head and neck region.7 The exposed bone appears largely avascular / ischaemic with a grey / brown discoloration. Associated clinical features may include a mucosal / cutaneous sinus tract, bone / gingival swelling, pain (from mild to severe), infection (local), sinusitis, trauma to adjacent soft tissues, tooth mobility, paraesthesia and or cervical lymphadenopathy.

Non-exposed BONJ was previously considered to be a transitory early-phase which was followed by mucosal fenestration and bone exposure. However there is increasing evidence that in approximately 50% of cases, it can exist as clinical entity / variant per se (never followed by bone exposure).8 Furthermore, only a third of these non-exposed cases may have associated radiological abnormalities. This is highly relevant for dentistry as this presentation can mimic dental disease, leading to misdiagnosis and unnecessary treatment.9

Biopsy is not usually needed to confirm the diagnosis, although...
bony sequestra can be sent for histopathology to assist in confirming the diagnosis and also to determine whether there is any secondary infection. Radiological features can be non-specific and do not always parallel clinical features. It is sometimes possible to see osteolysis / bone destruction, sclerotic changes, narrowing / sclerosis of the marrow space and / or pathological fractures. CT and MRI are superior to standard radiographic views in identifying necrotic areas and defining the extent of necrosis. Bone Scintigraphy is non-specific but very sensitive. CT, MRI and Scintigraphy can be particularly helpful in identifying necrotic areas in absence of obvious clinical features (bone exposure).

Of note, cases of osteonecrosis related to BPs have more recently been identified as the cause of atypical femur fractures and a number of cases confirmed as involving the external auditory canal area. A case affecting the thumb has also been described. A case affecting the thumb has also been described.

Management

There is currently no clear evidence for the efficacy of any intervention to manage BRONJ. Most studies report no real benefit from surgery, hyperbaric oxygen or Nd: YAG Laser. A variety of surgical approaches have been described, ranging from those that are relatively conservative (sequestrectomy +/- currettage), to resective surgery accompanied by flap reconstruction if required. More recent papers have reported some positive outcomes with surgical therapy involving large resection with margins in clinically uninvolved bone and have suggested this as a possible alternative to medical management. Palliative / symptomatic therapy is recommended in most cases. Some advise intermittent / long course of analgesics and / or antibiotics (with culture and sensitivity studies where needed). Local application of antibacterial agents (chlorhexidine; hydrogen peroxide) has also been suggested, accompanied by irrigation of fistulas with saline where appropriate. Unfortunately patients can be left with the necessity of chronic antibiotics and analgesic administration, recurrent / persistent oro-facial pain, necessity of regular visits for wound care and the impossibility of undergoing dental rehabilitation.

Risk reduction strategies

Comprehensive dental assessment should be undertaken prior to the commencement of bisphosphonate therapy. Emphasis is on reduction of mucosal trauma and avoidance of subsequent dental extractions. Preventive dental advice should be given, emphasizing the importance of reporting any symptoms such as loose teeth, pain, or swelling, as soon as possible. For those individuals who have already commenced BPs, there are currently no evidence-based guidelines to reduce the risk of developing BONJ. The lower risk of individuals on oral BPs as opposed to intravenous BPs should be considered. Most publications cite ‘expert opinion’ and the advice can be controversial and inconsistent. In general, dental extractions should be avoided where at all possible. Teeth should be stabilized with root canal treatment if there is a reasonable chance of this being successful. In cases where dental extractions cannot be avoided, there is no evidence supporting the discontinuation of bisphosphonates temporarily as the drugs persist in the skeletal tissues for years. There is also no conclusive evidence supporting the use of antibiotics or topical antiseptic prophylaxis in reducing the risk of BONJ. Straightforward extractions can be undertaken in primary care, although a second opinion can be sought when necessary.

Surgical extractions should be undertaken by a specialist. All patients should be advised of the risk pre-operatively and closely monitored post-operatively.

Conclusions

When prescribing bisphosphonates for individuals with thalassemia, awareness of the dental implications is essential so that patients can be appropriately advised of the risks. Ideally, patients should be seen by a dentist prior to commencing therapy, so that any dental risk factors for the development of BONJ can be removed. Subsequently, it is essential for these patients to receive regular dental review and preventative advice.

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