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This series aims to enhance the healthcare team's awareness of the importance of early detection by recognizing signs and symptoms of orofacial cancers and their management, and of prevention. It discusses treatment complications from surgery, radiotherapy (RT) and chemotherapy (CTX), summarizing the outcomes of a meeting on 'Oral Healthcare in People Living with Cancer' held in 2010, attended by 300 delegates from 33 countries – dentists, specialists, and Dental Care Professionals (DCPs), and the cancer support team. There is a considerable body of literature on oral cancer but very little is written on healthcare aspects of people living with cancer and a particular focus of this meeting was caring for survivors. The Faculty included European leaders in the field who have authored the series. The full peer-reviewed papers from the meeting are published in *Oral Oncology* 2010; **46**; 485–570.

## Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

# 17. Osteonecrosis

Patients with cancer may be liable to either osteoradionecrosis or osteochemonecrosis.

### Osteoradionecrosis

Radiotherapy (RT) in high doses involving the oral cavity, maxilla, mandible and salivary glands may result in several undesired reactions, of which osteoradionecrosis (ORN) is probably the worst. ORN is defined as exposed irradiated bone tissue that fails to heal over a period of 3 months without a residual or recurrent tumour.

The pathogenesis of ORN is not completely understood but it appears in hypoxic, hypovascular and hypocellular tissue, where there is tissue breakdown leading to a non-healing wound. There is no infection, but teeth in the field of irradiation might be the portal of entry for micro-organisms. ORN, as a radiation-induced fibro-atrophic mechanism, involves free radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodelling, and finally bone and tissue necrosis.

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### Risk factors

Risk factors for ORN include:

- **Radiation related factors:** eg total dose, photon energy, brachytherapy, field size, fractionation. With IMRT, only small partial volumes of the jaw are exposed to high radiation doses, so this may translate into a reduction of ORN.
- **Trauma and surgery:** risk is increased when tooth extractions are performed *after* RT, but there appears little increased risk when extractions are performed before. About 50% of ORN are 'spontaneous' and appear without a history of previous tooth removal. The single most important factor associated with ORN development is mandibular surgery.
- **Drug use:** alcohol and tobacco are risk factors for ORN. In contrast, corticosteroids or anticoagulants used before or after RT reduce the risk of ORN.

### Prevention of ORN

ORN is three times higher in dentate than in edentulous patients, which has led to a strategy of preventive extractions of all decayed and periodontally compromised teeth before jaw RT. However, since caries and periodontal disease are so common, there is controversy regarding whether such teeth should *always* be removed. Patients about to be treated with RT do need intensive preventive dental treatment but it is now generally accepted that teeth that really need to be extracted before RT are only those within the high-dose field that are unrestorable or have advanced periodontal involvement. The extractions must be done *before* RT, and patients who required multiple dental extractions or extensive surgical extractions, or both, can be given eight weeks of

pentoxifylline 400 mg twice daily with tocopherol 1000 IU, starting a week before the procedure, as prophylaxis.

### Management of ORN

Hyperbaric oxygen (HBO) has been advocated for pre-operative and post-operative treatment of ORN in high-risk patients having teeth extracted or other operations. A random, placebo-controlled, double-blind study failed to show benefits of HBO over placebo in recovery, in slowing ORN progression, or in relieving pain. Conservative management is preferred, not least since most patients have undergone major surgery before ORN arises and, as a consequence, usually wish to avoid additional jaw surgery, and up to 60% of early and localized cases of ORN resolve with medication and wound care alone. Pentoxifylline (PTX), an antioxidant methylxanthine derivative with an anti-tumour necrosis factor  $\alpha$  effect, administered for 6 months, or a combination of PTX and alpha tocopherol (vitamin E), another antioxidant, significantly accelerates healing. The development of myocutaneous flaps and microvascular free bone flaps allows for restoration of mandibular continuity and also brings non-irradiated soft tissue coverage with intact blood supply.

Other innovations are shown in Table 1.

### Osteochemonecrosis

Bisphosphonates (BP) are intravenously used (IV-BPs) for treatment of hypercalcaemia of malignancy, as well as prevention of skeletal-related events (SREs) and reduction of bone pain in cancer patients with osteolytic lesions. They are

Innovation		Comments
Physical	Ultrasound	<ul style="list-style-type: none"> <li>- Promotes angiogenesis</li> <li>- Stimulates osteoblasts</li> <li>- Induces cell proliferation and protein synthesis</li> <li>- Vasodilates</li> </ul>
	Distraction osteogenesis	<ul style="list-style-type: none"> <li>- Increases bone quantity, quality and neovascularization</li> </ul>
Chemical	Alpha tocopherol (vitamin E)	Protects cell membrane against peroxidation Inhibits TGF-β1 and procollagen gene expression
	Bone morphogenetic protein-1 (BMP-1, osteogenic protein-1; rhOP-1)	<ul style="list-style-type: none"> <li>- Promotes osteogenesis</li> </ul>
	BMP-2 (rhBMP-2)	<ul style="list-style-type: none"> <li>- Promotes osteogenesis</li> <li>- Induces osteoblast differentiation</li> <li>- Speeds healing</li> </ul>
	Fibroblast growth factor	<ul style="list-style-type: none"> <li>- Enhances angiogenesis</li> </ul>
	Pentoxifylline	Anti-tumour necrosis factor-α Vasodilates Inhibits inflammation, fibroblast proliferation and extracellular matrix formation <ul style="list-style-type: none"> <li>- Scavenges reactive oxygen</li> <li>- Heals fibrosis</li> </ul>

**Table 1.** Innovations in ORN treatment.

most commonly used in patients with multiple myeloma, breast, prostate, and lung cancers. Oral BPs are used mainly for prophylaxis of osteoporosis, and so are widely prescribed.

Bisphosphonates may cause osteochemonecrosis of the jaw (bisphosphonate-related osteonecrosis of the jaw, or BRONJ) – defined as *exposed necrotic bone appearing in the jaws of patients treated by BPs never irradiated in the head and neck area and that has persisted for more than 8 weeks*. Most cases (90%+) of BRONJ have been in patients with cancer who received IV-BPs, the cumulative incidence ranging from 1 in 10 to 1 in 1000 but the risk from oral BPs is far lower – less than 1 in 10000.

BPs inhibit the HMG-CoA

reductase (mevalonate) path, inhibiting osteoclasts, as well as directly inhibiting osteogenesis in bone-healing (Figure 1). In addition, nitrogen-containing BPs induce mucosal cell damage and impede wound healing. The main problem with BPs is the enormously long time they remain in bone and exert these effects – indeed for many years or decades.

### Risk factors for BRONJ

Risk factors include systemic and local factors:

- **Systemic factors** include:
  - the duration of BP exposure
  - the IV administration route
  - potent nitrogen-containing BPs (ie, zoledronate,

- pamidronate and ibandronate)
- smoking
- diabetes mellitus
- rheumatoid arthritis
- CYP2C8 gene diversity or reduced interleukin-17
- possibly chemotherapeutic agents, thalidomide, or bortezomib.

- **Local factors** include:

- Dental extractions – studies show at least 16-fold and up to 44-fold increased risk of BRONJ
- Denture wearing – there may be an almost 5-fold increased risk for patients taking zoledronate and also wearing dentures
- Periodontal disease – as a risk factor remains controversial.

### Prevention of BRONJ

Prevention is fundamental, since no cure is known. Studies have found an almost three-fold reduction of BRONJ related to zoledronate in myeloma patients after instituting preventive measures (dental screening, all dental work done at least six weeks before starting BPs). One protocol suggested to prevent BRONJ includes the raising of a flap before tooth extraction associated with a broad spectrum antibiotic started three days before, and the flap advanced for primary closure. Results were promising – no cases of BRONJ

Serum collagen telopeptide (CTX) levels, a reliable index of bone turnover rates might predict BRONJ risk but this is controversial. Perhaps CTX monitoring could help determine the best timing for a drug holiday.

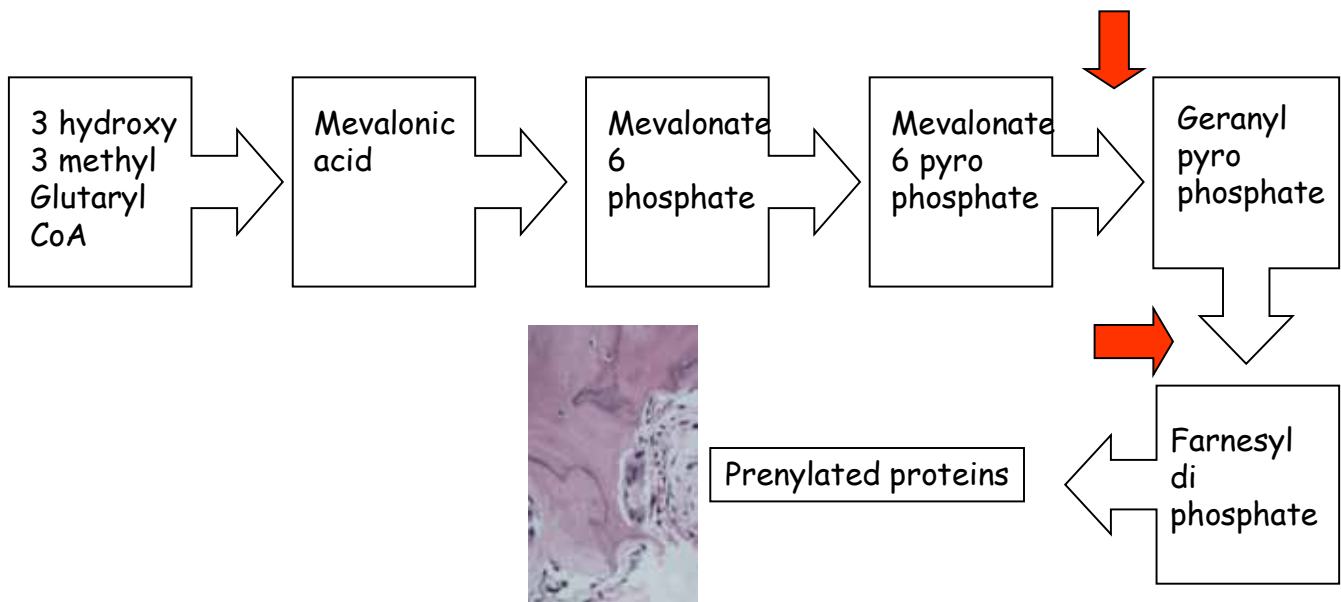
Prevention should thus include:

- Risk assessment;
- Patient counselling about risks;
- Avoiding elective oral surgery, including endosseous implant placement, or carrying out the treatment well before commencing BPs, or after a 6 month drug holiday.

### Management of BRONJ

BRONJ diagnosis is mostly from a history of BP therapy and typical clinical symptoms. BRONJ primarily affects the mandibular alveolar bone/mylohyoid ridge area, and features may include:

- Exposed bone;



**Figure 1.** Inhibitory action of bisphosphonates on mevalonic path.

- Loose teeth;
- Foul discharge;
- Pain;
- Fistulae.

Lamina dura sclerosis or loss, and periodontal ligament space widening may be early manifestations.

Because BRONJ has a variety of appearances on imaging, the diagnosis cannot be made from imaging alone,

though periapical and panoramic radiographs serve for initial screening. CT and MRI provide a more comprehensive evaluation. Bone scans can show abnormal radionuclide uptake 10 to 14 days before bone mineral loss radiographic changes are seen on conventional films. Tetracycline bone fluorescence has recently been used to visualize margins of osteonecrosis

more precisely: fluorescence-guided bone resection might improve the surgical therapy of BRONJ. HBO may be a possible adjunctive therapy for BRONJ but has yet to be studied.

Surgical resection generally appears not to benefit patients with BRONJ, so this has led to the restricted use of aggressive surgery in symptomatic patients with advanced BRONJ.

## Abstract

### WOULD YOU HAVE PASSED THIS TEST?

Depth and Distance Perception of Dentists and Dental Students. Dimitrijevic T, Kahler B, Evans G, Collins M, Moule A. *Oper Dent* 2011; **36**: 467–477.

Anyone who has taught in a dental school, particularly in the phantom-head classroom, or who has worked with new graduates in vocational training, will be aware that, whilst some students find restorative dentistry relatively easy, some find cavity preparation extremely difficult. Good perceptual and visual skills are essential, not only for gathering information, but also for judging positions, distances and the size of objects and shapes. The authors of this paper suggest that depth and

distance perception tests should be recommended for anyone entering the profession. Their supporting research investigated the ability of qualified dentists and different year-groups of dental students to estimate and reproduce small depths and distances. Various depth and distance perception tests were undertaken involving both estimation and writing tasks. Stereopsis and visual acuity were also assessed. It was found that both depth and distance were consistently over-estimated, although this tended to decrease with experience. All the student groups contained individuals with perceptual problems and who exhibited a large average error for all assessments. These problems may manifest in several task-oriented clinical procedures, for example

measurements on periodontal probes or the selection of appropriate diameter burs. Students with these problems will probably find it difficult to interpret verbal and written preclinical instructions and to acquire the necessary manual skills.

It was disturbing to note that the 163 dental students and 20 experienced dentists who took part in the research were all volunteers, since those who knew that they had such problems, perhaps receiving low marks in their clinical assessments, may have chosen not to take part. Also of significant concern is the authors' suggestion that those with difficulties could be identified and problems remedied, *if possible*, early in their course.

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