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Current trends in the medical management of osteoradionecrosis using triple therapy

J. Dhanda [a,*], L. Rennie [a], R. Shaw [b]

[a] *Department of Maxillofacial Surgery, Queen Victoria Hospital, East Grinstead, UK*
[b] *Department of Molecular and Clinical Cancer Medicine, North West Cancer Research Centre, The University of Liverpool Cancer Research Centre, UK*

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Abstract

Recent guidelines from the National Institute for Health and Care Excellence (NICE) have suggested that the medical management of osteoradionecrosis (ORN) of the jaws should be used in clinical trials only, and some drugs and therapeutics committees have withdrawn funds for such prescriptions. With increased scrutiny on the use of these agents, the aims of this study were to ascertain current trends in the presentation and management of ORN, with particular focus on which agents are being used.

Keywords: Osteoradionecrosis; Triple therapy; Medical management; Trends

Introduction

Osteoradionecrosis (ORN) of the jaws is a complication of radiation treatment for cancer of the head and neck. Its definition and classification have changed over the years,[1,2] and theories of its pathophysiology have evolved and led to new treatments.[3] Evidence for treatment, however, is largely based on retrospective or uncontrolled studies that are often open to considerable bias. There are substantial methodological hurdles in the few randomised controlled trials that have been done,[4] and because of this, the National Institute for Health and Care Excellence (NICE) has recommended that more modern approaches in the management of the condition (based on new concepts of pathophysiology), should be reserved for investigation in research and clinical trial settings only.[5]

Radiation of bone alters the normal physiological mechanisms that respond to systemic and local factors, and these mechanisms are essential to maintain a healthy and physiologically intact jaw. Early theories stated that ORN was the result of the exposure of bone to a critical dose of radiotherapy that caused local injury and subsequent infection.[6] The theory of "radiation-induced osteomyelitis", or secondary infection of devitalised bone, formed the basis for antimicrobial treatment.[7] Marx challenged this concept with his "hypoxic-hypocellular-hypovascular" theory, which began the use of hyperbaric oxygen therapy.[8–12] The value of hyperbaric oxygen to prevent and treat ORN is currently under investigation in two prospective, multicentre, randomised clinical trials based in the United Kingdom and Europe. The Hyperbaric Oxygen for the Prevention of Osteoradionecrosis (HOPON) and the Danish Head and Neck Cancer Association Trial 21 (DAHNCA21) clinical trials seek to address the relative paucity of well-managed studies on its use in patients with ORN.[13]

Delanian and Lefaix introduced the "fibroatrophic theory" of ORN in which radiation-induced fibrosis of both soft and

* Corresponding author.
E-mail addresses: jagdhanda@me.com (J. Dhanda), ljrennie@hotmail.co.uk (L. Rennie), Richard.Shaw@liverpool.ac.uk (R. Shaw).

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hard tissue was thought to result in the chronic non-healing of wounds in previously irradiated bone.[14] Fibroblast activation and dysregulation is the cornerstone of this theory and new treatments that targeted these mechanisms were proposed.[15] These offered targeted approaches to different aspects of the fibroatrophic model and included a free radical scavenger, tocopherol (vitamin E), which inhibited TNFα (tumour necrosis factor-alpha) and downregulated procollagen gene expression to reduce fibrosis. Pentoxifylline, which is a derivative of methylxanthine with an anti-TNFα effect is also used, as it has an inhibitory effect on fibroblast activation, and increases collagenase activity. Delanian et al used these agents in a phase II clinical trial with a bisphosphonate (clodronate) and the combination of all three agents was called triple therapy.[15] All patients with ORN improved at six months with a complete recovery in nearly all of them at eight months.[15] To date, there have been no randomised controlled trials of these agents in connection with mandibular osteoradionecrosis.

Patients with cancer of the head and neck now routinely seek restorative dental opinions before treatment, to make sure that any necessary extractions are completed well in advance of any radiotherapy to establish a preventative regimen.[16]

Conservative approaches in the management of ORN are reserved for patients with mild or no symptoms, who have early or moderate disease (Notani stage 1 in which ORN is confined to alveolar bone, or Notani stage 2 in which it is limited to alveolar bone or above the level of the inferior alveolar canal, or both).[17] In anticipation of progression of the disease some clinicians advocate early, simple operation, such as sequestrectomy or saucerisation, with local debridement and mucosal coverage. For more advanced disease (Notani stage III in which ORN is under the lower part of the inferior alveolar canal, with a fistula or bony fracture) resection and reconstruction with free tissue transfer is advocated.[18]

The aims of this study were to ascertain current trends in the presentation and management of ORN with particular focus on which agents are being used for medical management, if this is influenced by the symptoms and severity of disease, and the numbers of patients treated. This study will also ascertain whether previous experience of recruiting to trials in this field influences the willingness of clinicians to participate in a trial that compares the medical management of ORN with other treatments.

Method

We devised an online survey using SurveyMonkey® (San Mateo, CA, USA) and disseminated it through the oncology and reconstruction subspecialty interest groups of the British Association of Oral and Maxillofacial Surgeons (BAOMS), along with online forums for oral and maxillofacial higher surgical trainees (Fig. 1). We used it to verify the grade of the participant, how many patients with ORN they had assessed, and whether they perceived the condition as an increasing problem. We established the number of patients treated in each centre/year and asked how many of them were managed with drugs. We asked them to give the number of patients/unit who had medical management and the types of cases based on symptoms and severity (Notani classification). For those who treated ORN with drugs, data relating to the agents used and the use of induction-phase antibiotics or steroids were collected in addition to the types of surgical management also offered. We also asked about the participants' awareness of the new NICE guidelines, their willingness to recruit to a national trial, and their previous experience of recruitment to existing ORN trials. Finally, we asked them if they felt that there was a role for medical management in the prevention of ORN.

Statistical analyses were done using the chi squared test to ascertain the differences between the types of agents used and the number of cases seen/year and the tendency to recruit to clinical trials. A Fisher's exact test was used to ascertain the differences between the types of agents used and the awareness of the NICE guidelines. A Kruskal–Wallis test was used to compare numbers of patients who had presented with ORN and whether participants thought that ORN was an increasing problem (yes/no). Statistical packages used included SPSS Statistics for Windows, version 21 (IBM Corp) and Microsoft Excel version 15.41, (Microsoft Corp). Probabilities of less than 0.05 were accepted as significant.

Table 1
Responses from 101 participants who completed the survey on the number of patients/year that present with osteoradionecrosis and the treatments used.

	No. of responses
No. of cases seen/year:	
<5	12/82
6–10	41/82
>10	29/82
No. of patients treated with a free flap/year	
<5	46/59
6–10	9/59
>10	4/59
No. of patients treated with debridement and local flaps/year	
<5	36/63
6–10	20/63
>10	7/63
No. of patients treated with drugs:	
<one-third	15/54
One to two-thirds	12/54
> two-thirds	27/54

Results

A total of 101 responses were returned from 31 units nationwide. Most participants (65/95) were consultants and 19/25 were senior trainees. A total of 91/99 had treated ORN and 67/95 stated that it was an increasing problem in their medical practice. Table 1 shows the number of patients treated and the treatments given. A total of 11/53 treated all patients with

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