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Is there a role for pentoxifylline tocopherol in the management of advanced osteoradionecrosis of the jaws with pathological fractures? Case reports review of the literature

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O. Breik, S. Tocaciu, K. Briggs, S. Tasfia Saief, S. Richardson: Is there a role for pentoxifylline tocopherol in the management of advanced osteoradionecrosis of the jaws with pathological fractures? Case reports review of the literature. Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx.

Abstract. Osteoradionecrosis (ORN) is an infrequent but serious complication of radiotherapy, especially in the head and neck region. It is a slowly progressive condition, with management in the early stages focused on symptom control, and surgery usually reserved for advanced ORN. However, established ORN is difficult to treat. The role of hyperbaric oxygen therapy has recently been contested. The use of pentoxifylline in the management of ORN was first described by Delanian in 2004, but its benefits have not been replicated in other studies. In cases of advanced ORN with pathological fractures, many centres still advocate surgical resection and reconstruction. However, in this group of patients who often have multiple medical comorbidities, many of whom have previously undergone significant surgery, a resective plan is not always ideal. This paper presents two successful cases of bony union after the use of pentoxifylline and tocopherol to manage grade III ORN of the mandible. Both patients had pathological fractures and orocutaneous fistulas and were deemed unsuitable for surgery. The possible reasons for the success of pentoxifylline and tocopherol are discussed, and a review of the current literature evidence of similar cases is presented. Pentoxifylline and tocopherol should be considered for the management of advanced ORN where surgical management is not appropriate.

Key words: osteoradionecrosis; ORN; radiotherapy; pentoxifylline; tocopherol; osteonecrosis; PENTO; PENTOCLO.

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Osteoradionecrosis (ORN) of the jaws is one of the most serious complications of radiotherapy to the head and neck for the management of oral and oropharyngeal cancer. The incidence of ORN is believed to be approximately 7.4% of patients[1], and ORN is most common in patients treated with over 60 Gy of radiation, patients of advanced age, smokers, those currently using alcohol, and those with poor nutritional status[2]. Medical comorbidities such as diabetes mellitus, hypertension, and collagen vascular diseases have also been found to increase the risk of developing ORN[3]. Dental patient risk factors include active periodontal disease and extractions[4,5]. The mandible has been found to be affected more commonly than the maxilla[1,6], by a factor of 24[7]. Tumour-related risk factors for developing ORN include advanced stage at diagnosis (grade III) and high-risk sites such as the tongue, floor of the mouth, alveolus, retromolar trigone, and tonsil. These primary sites have been reported to be associated with a higher risk of developing ORN as the radiotherapy field would inadvertently include the tooth-bearing alveolus[3].

Several definitions of ORN exist. The definition proposed by Marx in 1983 described ORN as ''an area greater than one centimetre of exposed bone in a field of radiation that has failed to show any evidence of healing for at least 6 months''[8,9]. Harris amended the definition in 1992 to reduce the duration of bone exposure and to include the surrounding soft tissue, as follows: ''exposed and necrotic bone associated with ulcerated or necrotic surrounding soft tissue which persists for greater than three months, in an area that has been previously irradiated and is not caused by tumour recurrence''[10]. The need to exclude a malignancy is crucial, as it prompts the practitioner to perform a biopsy, thereby avoiding misdiagnosis of tumour recurrence, which can present with a similar clinical picture.

The pathogenesis of ORN is not clear, and many theories have been proposed, which have guided treatment algorithms. Watson and Scarborough in 1938 first identified three crucial factors in the development of ORN: radiation, trauma, and infection[11]. In 1970, Meyer built on this and proposed that antibiotics be used in conjunction with any surgery conducted on patients exposed to previous radiotherapy[12,13]. Marx built on this further in 1983 by proposing that ORN was not an infection, but instead a deficiency in the homeostatic and metabolic capacity of bone as a result of irradiation. Marx proposed that radiation caused the jaw bone to become hypoxic, hypocellular, and hypovascular, leading to reduced healing capacity and remodelling potential, and resulting in the formation of a chronic non-healing wound[8,9].

In 2004, Delanian and Lefaix proposed the fibroatrophic theory of ORN pathogenesis[14]. This theory proposed that irradiation results in activation and dysregulation of fibroblasts, which causes fibroatrophy of the cellular bone marrow[14]. This was hypothesized to occur in three phases. The first phase is one of 'pre-fibrosis' where there is chronic inflammation. This is followed by an 'organized phase' of fibrosis and then a 'fibroatrophic phase' in which there is gradual loss of bone marrow cells. Delanian et al. suggested that there may be two pathways to this radiation-induced fibrosis. The first pathway is one of gradual hypoxia similar to what Marx described. The second pathway is the stromal theory, which suggests that radiotherapy increases reactive oxygen species in the bone, which then dysregulate fibroblasts and induce metaplasia to myofibroblasts[15].

The management of ORN has been controversial and highly variable between centres. Small areas of exposed bone have traditionally been treated with conservative management, consisting of mouthwash, analgesia, and antibiotics for acute infective exacerbations. Local debridement and sequestrectomy may be offered for grade II ORN, and resection is usually reserved for late-stage grade III ORN.

Hyperbaric oxygen therapy (HBO) became widely used after the work by Marx[8,9]. Marx proposed the use of HBO in the management of ORN based on its neovascularization potential[8,9]. He developed a treatment protocol for patients (the Wolford Hall HBO protocol), in which they underwent 30 dives of 100% oxygen at 2.4 atmospheres for 90 minutes. This was followed by sequestrectomy or debridement for stage II or resection for stage III ORN cases, followed by a further 30 dives[8,9]. Any reconstruction was deferred for patients with refractory ORN not responding to HBO. Although Marx described good results, these have not been replicated by other authors, and in fact some studies have shown worse results after reconstruction in ORN patients who have had previous HBO compared to those who have not[16]. Even the role of HBO in the prevention of ORN has been questioned in recent times based on more recent studies showing disappointing results of HBO compared to placebo[17].

HBO is not without its complications[18,19], and many side effects have been described, mainly caused by barotrauma (e.g., hearing loss, visual changes, and seizures). Hence, HBO is relatively contraindicated in patients at risk of barotrauma (e.g., those with pneumothorax or eustachian tube dysfunction). HBO can also be hazardous to patients with certain oxygen-sensitive states such as asthma/chronic obstructive pulmonary disease, congenital spherocytosis, or those with claustrophobia.

The use of pentoxifylline, tocopherol, and clodronate together (PENTOCLO) in the management of ORN was first proposed by Delanian and Lefaix[14]. Here, the specific agents were thought to counteract the development of radiation-induced fibrosis. Pentoxifylline was suggested to improve blood viscosity and flow, improving the vascularity of affected tissues. Tocopherol (a vitamin E analogue) is an anti-oxidant and is thought to scavenge reactive oxygen species. Lastly, clodronate, a first-generation non-nitrogenous bisphosphonate, was added in non-responsive cases and to promote osteoblast differentiation and osteogenesis[15].

The benefits of PENTOCLO were first described in a case of sternal ORN in a female patient who had previously undergone radiotherapy for breast cancer[20]. Subsequently, PENTOCLO was used successfully in 16 of 18 patients with mandibular ORN of the jaws not responding to conservative therapy alone. Of these patients, four had stage III ORN with pathological fractures. Although the paper did not discuss these more advanced patients in significant detail, it appears that all of the patients had pathological fractures without 'shifting' or without displacement[21]. A subsequent study by Delanian et al. in 2011 evaluated the role of the PENTOCLO protocol in the management of 54 patients[15]. Of these, 36 were classified as having advanced ORN (Epstein III with fistula, fracture, or osteitis). However, it was unclear how many patients actually had fractures, and in the conclusions, the authors advised that surgical management should still be considered in patients with fractures without displacement.

Unfortunately, these favourable results could not be replicated by many. Notably, the Portsmouth UK experience published in 2012 showed no benefit of pentoxifylline and tocopherol when used in similar patients with early stage mandibular ORN[21]. Hence, there has been resistance to adopting its use in many units. Also, due to the paucity of studies with similar

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success rates as the Delanian studies, most protocols published so far in the oral and maxillofacial and head and neck literature have advised excluding patients with pathological fractures, as they have been deemed unlikely to respond to treatment[13,22].

Overall, the use of pentoxifylline and tocopherol has been an exciting development in the management of ORN, and this combination has even been shown to successfully treat cases of medication-related osteonecrosis of the jaws by several groups[23–25], suggesting that these agents still show some promise in reversing a variety of forms of osteonecrotic damage to the jawbones. The most recent meta-analysis and systematic review of the literature by Kolokythas et al. (2019) suggests that the literature supports the use of pentoxifylline and tocopherol in ORN of the jaws but that additional studies are needed to further validate its use[26].

The purpose of this paper is to report two cases in which pentoxifylline and tocopherol was used in patients with advanced ORN with pathological fractures, who showed subsequent bony union and thereby avoided the need for resection and reconstruction. A review of the current evidence for the use of pentoxifylline and tocopherol in such advanced cases is also presented in the Discussion.

Methods and results

The use of pentoxifylline and tocopherol for the management of early ORN, as well as for symptomatic relief, is considered for patients attending the Oral and Maxillofacial Unit at Monash Health. In two instances, this treatment was used for patients with late-stage ORN (Notani grade 3[27]) with pathological fractures and orocutaneous fistulas who had either refused surgery or been deemed unsuitable for further surgery. The cases of these two patients, who showed surprising results with unexpected bony union following the use of pentoxifylline and tocopherol, are described here. The possible reasons for the successful results and potential future applications of pentoxifylline and tocopherol in the management of advanced ORN of the jaw are discussed. The patients are de-identified, and data were obtained from a retrospective review of the records. Therefore, this study was exempt from ethical board review.

Case one

A 59-year-old female patient underwent chemoradiotherapy for a T3N2b moderately differentiated squamous cell carcinoma of the right tonsillar fossa in 2005. This was on a background of smoking 30 cigarettes a day and heavy alcohol intake. Her treatment regimen involved 70 Gy of radiation, carboplatin, and 5-flurouracil. She was subsequently lost to follow-up and then presented 10 years later (in 2015) to an oral and maxillofacial surgeon with pain and swelling overlying the right mandibular body. Intraoral examination revealed an area of exposed bone 2 cm × 2 cm and she was found to have a pathological fracture of the right mandibular body (Fig. 1). Biopsy of the bone and surrounding oral mucosa excluded recurrence of her carcinoma and confirmed grade III (Notani classification) ORN.

The patient refused further surgery and remained on conservative therapy for 24 months (chlorhexidine mouthwash, oral analgesia, and intermittent courses of oral antibiotics to treat any infective exacerbations). The patient was subsequently reviewed in 2017 with persistent pain, and a panoramic radiograph demonstrated worsening osteolysis around the pathological fracture (Fig. 2). Furthermore, she had developed a 1 cm × 1 cm area of erythema and swelling in the skin overlying the right mandibular body, which eventually broke down to form an orocutaneous fistula. She was initially treated with two courses of antibiotics (first course of 10 days of oral amoxicillin with clavulanic acid twice daily, followed by 10 days of clindamycin 300 mg four times daily) to reduce the discharge from the orocutaneous fistula and help resolve the infection, with no improvement. Clinically, the fracture was not mobile on examination, but she did report clicking from the angle of the mandible on opening and closing. As she was still not a suitable surgical candidate, the patient was commenced on pentoxifylline 400 mg and tocopherol 500 IU twice daily and advised to stay on a soft diet. She reported a significant improvement in her pain at 3 months, with a reduction in the clicking noises, but persistence of the orocutaneous fistula. She continued the pentoxifylline for a further 3 months. On subsequent review, the patient had no further clicking noises from the fracture site and she had complete resolution of the orocutaneous fistula. Clinically, the area of exposed bone intraorally had reduced in size to approximately 1 cm × 1 cm. A panoramic radiograph at 6 months showed evidence of bone formation at the site of the pathological fracture (Fig. 3). The pentoxifylline and tocopherol were stopped after 6 months due to patient preference.

On review at 12 months since commencing pentoxifylline and tocopherol, there was no recurrence of the orocutaneous fistula, and the patient had no symptoms of the

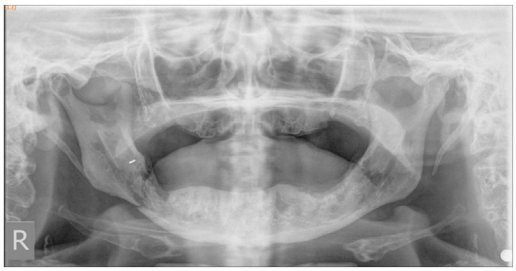

Fig. 1. Panoramic radiograph showing pathological fracture of the right mandibular body, and sclerotic bone changes consistent with previous radiotherapy.

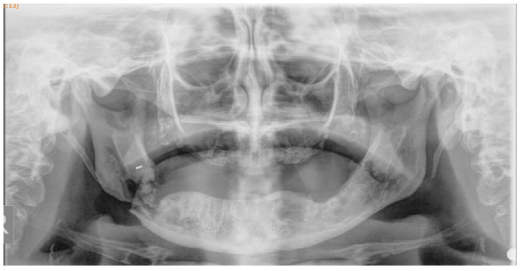

Fig. 2. Panoramic radiograph showing worsening osteolysis at the site of pathological fracture (right mandibular body).

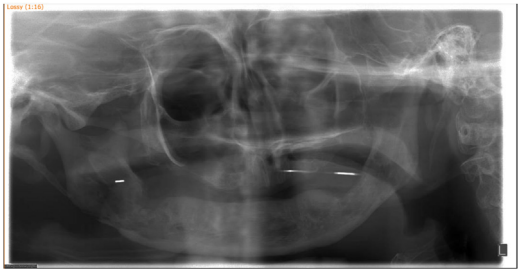

Fig. 3. Panoramic radiograph after 3 months of pentoxifylline and tocopherol showing evidence of bone formation.

pathological fracture. The area of exposed bone intraorally was stable, with no evidence of progression. She remains on close clinical follow-up.

Case two

A 44-year-old man underwent a right hemiglossectomy, bilateral selective neck dissection, and reconstruction with a radial forearm free flap for a T2N0M0 squamous cell carcinoma of the right tongue in 2003. The patient also underwent adjuvant chemoradiotherapy. He subsequently moved to a different city in Australia and was lost to follow-up.

In 2014, some 11 years later, the patient presented to an oral and maxillofacial surgeon with a left-sided orocutaneous fistula, pain, and paraesthesia of the inferior alveolar nerve. Clinically he had a small area of exposed bone and an orocutaneous fistula. A panoramic radiograph demonstrated bony sclerosis of the mandible, but no fracture (Fig. 4). He was referred for HBO as per the Marx protocol and underwent 30 dives, but had continual infections, chronic pain, and persistent orocutaneous fistula. In January 2016, the patient underwent debridement of the left mandibular necrotic bone and removal of infected teeth on the affected side. Four months later, he reported persistent pain, as well as discharge from the orocutaneous fistula. A panoramic radiograph now revealed a pathological fracture (Fig. 5). Following this, the pathological fracture and the orocutaneous fistula persisted, requiring multiple courses of antibiotics due to recurrent exacerbations. Clinically the fracture was not mobile, likely due to the highly fibrotic surrounding radiotherapy affected tissue.

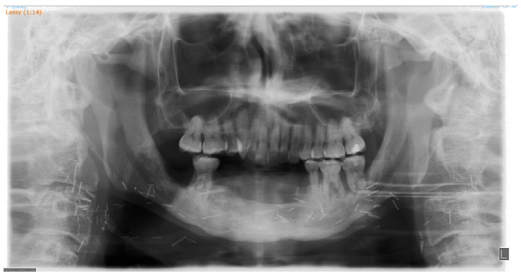

Fig. 4. Baseline panoramic radiograph of a patient at the time of diagnosis of osteoradionecrosis in 2014.

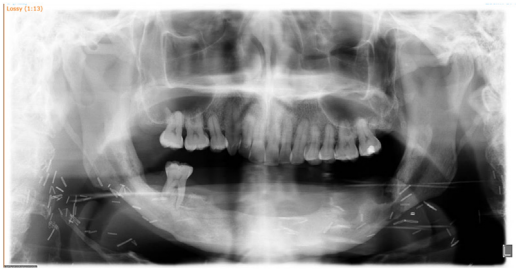

Fig. 5. Panoramic radiograph 4 months after surgical debridement and removal of teeth, showing pathological fracture of the left mandibular body.

Surgical resection and reconstruction was discussed with the patient in June 2016, but deferred due to patient preference. As a temporary measure and for symptomatic relief, the patient was commenced on pentoxifylline 400 mg and tocopherol 500 IU twice daily. Over the next 10 months, the patient reported significant improvements. Clinically he had no mobility of the mandible, good oral function, no exposed bone intra-orally, and resolution of the orocutaneous fistula. A panoramic radiograph showed evidence of bone healing. At the most recent review, more than 16 months after commencing pentoxifylline and tocopherol, a new panoramic radiograph (Fig. 6) and computed tomography showed persistent bony union at the site of the previous fracture and no recurrence of the orocutaneous fistula. The patient remained on pentoxifylline and tocopherol for 12 months.

Discussion

Advanced full thickness ORN (Notani grade III), especially in the setting of a pathological fracture or an orocutaneous fistula, has traditionally been treated with surgical resection and vascularized free flap reconstruction, with good results reported in some studies[28]. However, there are concerns regarding operating within an irradiated field, and many of our patients are unsuitable for resective and reconstructive therapy, so conservative management and supportive care remain a commonly adopted treatment for ORN. In addition, many patients refuse further surgery. In these settings, there may be a role for the implementation of pentoxifylline and tocopherol.

Pentoxifylline and tocopherol was first used in the management of early ORN as the two agents directly counteracted the proposed fibroatrophic pathogenesis of ORN[14]. Initial studies have shown good results and no significant adverse effects from the medications[14]. The role of pentoxifylline and tocopherol in advanced ORN, where patients are unsuitable for resection, has been reported in the work of Delanian et al.[15,20]. In the first study, six patients with pathological fractures were included, and five showed an improvement in staging, with resolution of the pathological fracture[20]. The authors clearly reported that these patients had pathological fractures without shifting (i.e., undisplaced, non-mobile fractures).

Apart from the studies by Delanian et al., several maxillofacial surgery units have reported their outcomes in both retrospective and prospective studies, which

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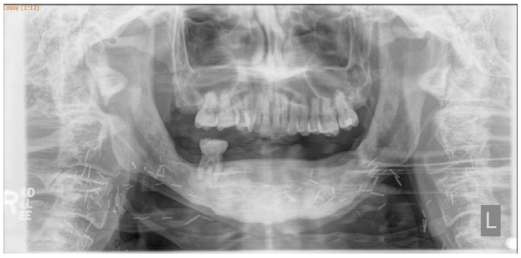

Fig. 6. Panoramic radiograph 16 months after the commencement of pentoxifylline showing evidence of fracture healing.

have been summarized in a recent systematic review[29]. Some of the studies included in that systematic review included patients with advanced ORN and their outcomes with the use of pentoxifylline and tocopherol[20,30–32]. Of note, the majority of the investigators avoided the use of clodronate in their treatment protocols, mainly due to their experience with bisphosphonate-induced osteonecrosis of the jaws[21]. We avoided clodronate in our patients for the same reasons. Of these studies, only the one by McLeod et al. published in 2012 clearly included patients with pathological fractures managed with pentoxifylline and tocopherol, and they found that use of pentoxifylline and tocopherol only improved the staging from active progressive disease with a pathological fracture to chronic, non-progressive disease with a persistent pathological fracture[21]. The remaining papers mentioned above reported that advanced ORN with pathological fractures required resection and free vascularized tissue transfer[22,32].

The two cases presented in this paper showed promising improvements in both the pathological fracture and the orocutaneous fistula in patients who were managed non-operatively with pentoxifylline and tocopherol, avoiding the need for resection and vascularized free tissue transfer. Such results have not been reported by many authors.

What contributed to the unexpected improvement in the patients reported in this study? It is difficult to explain such results; however, one obvious feature is that in both cases the pathological fractures were not mobile, similar to those described by Delanian et al.[33]. Does a pathological fracture that is not mobile increase the potential for the anti-fibrotic medications to minimize the progressive osteolysis and abnormal fibrous bony formation around the fracture sites? These findings may warrant consideration of stabilization of early pathological fractures with external fixation or even trans-mucosal fixation. Of course, there is the concern that external fixation especially may lead to orocutaneous fistula formation, so novel ideas are needed to determine the best way to stabilize the fracture segments to encourage healing, especially in cases where vascularized free tissue transfer is not possible due to patient comorbidities or patient preference. Prior to embarking on such treatment considerations, further examples of bony healing due to pentoxifylline and tocopherol therapy are needed to demonstrate its efficacy in these advanced cases of ORN.

Although these cases demonstrate potentially promising effects of pentoxifylline and tocopherol in advanced ORN, several questions remain. Why and how does an anti-fibrotic agent help in patients whose bone has long been affected by the radiotherapy? After establishing ORN, is the abnormal fibroatrophic process not already irreversible? The only possible explanation for the potential beneficial effects of an anti-fibrotic agent like pentoxifylline is that in the setting of acute inflammation, an orocutaneous fistula, or a pathological fracture, additional abnormal fibrosis further compromises the healing process, preventing healing. Hence, providing the anti-fibrotic agent may facilitate a more favourable healing process that leads to improvement and potential resolution. In addition, some studies are demonstrating osteogenic effects of pentoxifylline. Although this mechanism is still poorly understood, is it possible that the administration of pentoxifylline promotes osteogenesis, which could explain its potential effect in promoting fracture healing[34]. Further research is needed to fully understand the mechanism of these agents in the setting of ORN in order to explain the potentially beneficial effects.

Another question is how long should the patient remain on pentoxifylline and tocopherol? In the cases presented herein, the first patient was on the agents for 6 months, while the second was on them for 12 months. It is not clear from other studies how long each patient was on the agents. From experience and the results of these studies, the present authors would advise considering a 12-month regimen. In the recent meta-analysis on the topic by Kolokythas et al., 2018[24], the authors advised considering pentoxifylline and tocopherol for at least 6 months and then for as long as regression is observed. However, further well-designed prospective studies are needed to determine the ideal treatment length.

Pentoxifylline and tocopherol may have a role in the management of advanced stage ORN of the jaw with pathological fracture. In the cases presented in this paper, both patients showed union of the pathological fracture, demonstrated improvements in pain, and their orocutaneous fistulas showed signs of significant healing. The use of pentoxifylline and tocopherol for advanced ORN should be explored further, as it may provide an alternative to surgical resection.

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Competing interests

None.

Ethical approval

Not applicable.

Patient consent

Not required.

References

1. Peterson DE, Doerr W, Hovan A, Pinto A, Elting LS, Spijkervet FK, Brennan MT. Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies. *Support Care Cancer* 2010;**18**:1089–98. http://dx.doi.org/10.1007/s00520-010-0898-6.
2. Owosho AA, Tsai CJ, Lee RS, Freymiller H, Kadempour A, Varthis S, Sax AZ, Rosen EB, Yom SK, Randazzo J, Drill E, Riedel E, Patel S, Lee NY, Huryn JM, Estilo CL. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): the Memorial Sloan Kettering Cancer Center experience. *Oral Oncol* 2017;**64**:44–51.
3. Balogh JM, Sutherland SE. Osteoradionecrosis of the mandible: a review. *J Otolaryngol* 1989;**18**:245–50.

4. Clayman L. Clinical controversies in oral and maxillofacial surgery: part two. Management of dental extractions in irradiated jaws: a protocol without hyperbaric oxygen therapy. *J Oral Maxillofac Surg* 1997;**55**:275–81.
5. Vudiniabola S, Pirone C, Williamson J, Goss AN. Hyperbaric oxygen in the therapeutic management of osteoradionecrosis of the facial bones. *Int J Oral Maxillofac Surg* 2000;**29**:435–8.
6. Store G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. *Clin Otolaryngol Allied Sci* 2000;**25**:378–84.
7. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. *Int J Oral Maxillofac Surg* 2011;**40**:229–43.
8. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;**41**:351–7.
9. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg* 1983;**41**:283–8.
10. Harris M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. *Br J Oral Maxillofac Surg* 1992;**30**:313–8.
11. Watson WL, Scarborough JE. Osteoradionecrosis in intraoral cancer. *Am J Roentgenol Radium Ther* 1938;**40**:524–34.
12. Meyer I. Infectious diseases of the jaws. *J Oral Surg* 1970;**28**:17–26.
13. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. *Br J Oral Maxillofac Surg* 2008;**46**:653–60.
14. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. *Radiother Oncol* 2004;**73**:119–31.
15. Delanian S, Chatel C, Porcher R, Depondt J, Lefaix JL. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline–tocopherol–clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;**80**:832–9.
16. Gal TJ, Yueh B, Futran ND. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. *Arch Otolaryngol Head Neck Surg* 2003;**129**:72–6.
17. Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P, Chevret S. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;**22**:4893–900.
18. Heyboer M, Sharma D, Santiago W, McCulloch N. Hyperbaric oxygen therapy: side effects defined and quantified. *Adv Wound Care* 2017;**6**:210–24.
19. Kaur J, Hay KD, Macdonald H, Rich AM. Retrospective audit of the use of the Marx protocol for prophylactic hyperbaric oxygen therapy in managing patients requiring dental extractions following radiotherapy to the head and neck. *N Z Dent J* 2009;**105**:47–50.
20. Delanian S, Lefaix JL. Complete healing of severe osteoradionecrosis with treatment combining pentoxifylline, tocopherol and clodronate. *Br J Radiol* 2002;**75**:467–9.
21. McLeod NM, Pratt CA, Mellor TK, Brennan PA. Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience. *Br J Oral Maxillofac Surg* 2012;**50**:41–4.
22. Lyons A, Osher J, Warner E, Kumar R, Brennan PA. Osteoradionecrosis—a review of current concepts in defining the extent of the disease and a new classification proposal. *Br J Oral Maxillofac Surg* 2014;**52**:392–5.
23. Epstein MS, Wicknick FW, Epstein JB, Berenson JR, Gorsky M. Management of bisphosphonate-associated osteonecrosis: pentoxifylline and tocopherol in addition to antimicrobial therapy. An initial case series. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;**110**:593–6.
24. Magremanne M, Reychler H. Pentoxifylline and tocopherol in the treatment of yearly zoledronic acid-related osteonecrosis of the jaw in a corticosteroid-induced osteoporosis. *J Oral Maxillofac Surg* 2014;**72**:334–7.
25. Owosho AA, Estilo CL, Huryn JM, Yom SK. Pentoxifylline and tocopherol in the management of cancer patients with medication-related osteonecrosis of the jaw: an observational retrospective study of initial case series. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016;**122**:455–9.
26. Kolokythas A, Rasmussen JT, Reardon J, Feng C. Management of osteoradionecrosis of the jaws with pentoxifylline–tocopherol: a systematic review of the literature and meta-analysis. *Int J Oral Maxillofac Surg* 2019;**48**:173–80.
27. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, Nakamura M. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck* 2003;**25**:181–6.
28. Glanzmann C, Gratz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. *Radiother Oncol* 1995;**36**:94–100.
29. Martos-Fernandez M, Saez-Barba M, Lopez-Lopez J, Estrugo-Devesa A, Balibrea-Del-Castillo JM, Bescos-Atin C. Pentoxifylline, tocopherol, and clodronate for the treatment of mandibular osteoradionecrosis: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;**125**:431–9.
30. Patel V, Gadiwalla Y, Sassoon I, Sproat C, Kwok J, McGurk M. Use of pentoxifylline and tocopherol in the management of osteoradionecrosis. *Br J Oral Maxillofac Surg* 2016;**54**:342–5.
31. Bohn JC, Schussel JL, Stramandinoli-Zanicotti RT, Sassi LM. Tissue repair in osteoradionecrosis using pentoxifylline and tocopherol—report of three cases. *Oral Maxillofac Surg* 2016;**20**:97–101.
32. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: experience from a regional head and neck unit. *Br J Oral Maxillofac Surg* 2014;**52**:356–62.
33. Delanian S, Depondt J, Lefaix JL. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. *Head Neck* 2005;**27**:114–23.
34. Labib GS, Farid RM. Osteogenic effect of locally applied pentoxifylline gel: in vitro and in vivo evaluations. *Drug Deliv* 2015;**22**:1094–102.

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