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# Use of pentoxifylline and tocopherol in the management of osteoradionecrosis

Vinod Patel [a], Yusuf Gadiwalla [a], Isabel Sassoon [b], Chris Sproat [a], Jerry Kwok [a], Mark McGurk [c,*]

[a] *Oral Surgery Dept, Floor 23, Guys Dental Hospital, London Bridge, London, SE1 9RT*
[b] *Department of Informatics, King's College London, Strand, London, WC2R 2LS*
[c] *Department of Oral and Maxillofacial Surgery, Atrium 3, 3rd Floor, Bermondsey Wing, Guy's Hospital, London, SE1 9RT*

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**Abstract**

Osteoradionecrosis (ORN) is a complication of radiotherapy, and is difficult to manage once established. However, its pathogenesis has been reinvestigated, and it is now thought to be potentially amenable to treatment with pentoxifylline and tocopherol (vitamin E). We made a retrospective analysis of 62 patients with established ORN who were treated in this way. When only pentoxifylline and vitamin E was used ORN resolved in 14/25 (56%) but paradoxically, when it was combined with antibiotics, only 6/22 resolved (27%). The next stage would ideally be to incorporate the treatment in a randomised clinical trial against both standard antibiotic treatment and hyperbaric oxygen.


*Keywords:* Pentoxifylline; Tocopherol; Osteoradionecrosis

## Introduction

Osteoradionecrosis (ORN) is a complication that may follow radiotherapy for head and neck cancer and it has lifelong repercussions. Historically the incidence has ranged from 2%-22%,[1–3] but a recent systematic review by Nabil and Samman[4] of 5742 patients estimated a general risk of 2%, which may increase if patients have additional risk factors. However, the risk of ORN is changing as new ways of delivering radiotherapy are introduced, such as intensity modulated radiation therapy (IMRT), together with the increased use of chemotherapy. The initial impression is that the combination of chemoradiotherapy may increase the risk of fibrosis and ORN.

Once ORN is established and symptomatic it can be difficult to manage, particularly conservatively. Treatments include antibiotics, which will alleviate pain for a transient period of time, and then debridement, the outcome of which is unpredictable. Historically hyperbaric oxygen was the treatment of choice, but it is difficult to procure, treatment is protracted, and the results are equivocal. Pentoxifylline and tocopherol (vitamin E) have also been suggested, their use being based on the newly-proposed pathogenesis for ORN, which is based on radiation-induced fibrosis.[5] It is thought that the fibrotic reaction may be ameliorated by antioxidants and antifibrotic treatment in the form of pentoxifylline and tocopherol.

Here we describe the outcomes of ORN in a single unit in which patients were treated with the two drugs and which, to our knowledge, is the largest series published to date.

* Corresponding author.
*E-mail addresses:* Vinod.Patel@hotmail.co.uk (V. Patel), yusuf.gadiwalla@nhs.net (Y. Gadiwalla), isabel.sassoon@kcl.ac.uk (I. Sassoon), Chris.Sproat@gstt.nhs.uk (C. Sproat), Jerry.Kwok@gstt.nhs.uk (J. Kwok), Mark.mcgurk@kcl.ac.uk (M. McGurk).

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## Method

We made a retrospective analysis (January 2008 –February 2014) of the head and neck oncology database to identify patients with ORN. The electronic prescription log held in the hospital pharmacy was requested to identify patients to whom pentoxifylline and tocopherol had been prescribed, and the clinical records were reviewed. Pentoxifylline and tocopherol have been used for ORN at Guy's Hospital since 2008, so cases before this date were excluded.

The dose of pentoxifylline was 400 mg twice daily and tocopherol 1000 IU once daily. ORN was defined as bone in the mandible or maxilla that had been exposed for longer than 2 months, together with a previous history of radiotherapy to the head and neck. Sixty-two patients were identified, and pentoxifylline and tocopherol were used as first line management in all cases. Antibiotics were given simultaneously only if there was a clinical evidence of infection. Additional management (surgical debridement, hyperbaric oxygen, or resection) were used at a later date when it was felt that the two drugs alone were insufficient. They were, however, continued together with any additional management.

Data was collected from clinical and radiographic records and entered in a database that included personal details and clinical history. The grading system described by Notani et al was used to stage the ORN.[6]

Our primary end point was resolution of the ORN, which was defined as the development of stable mucosal coverage over previously exposed bone together with no clinical symptoms. Secondary endpoints were progression and persistence of ORN, but symptoms improved.

The data was analysed in R v. 3.1.2.[24] Quantitative variables are expressed as mean (range). Qualitative variables with more than five levels were grouped into categories to make the results easier to understand.

## Results

During the period 2008-2014, 62 patients (45 male and 17 female, mean (range) age 60 (40-83) years) were identified as having ORN. The most common site of the primary tumour was the oropharynx (n=25) followed by the oral cavity (n=24). The remainder were in the hypopharynx (n=2), nasopharynx (n=3) and miscellaneous (n=8).

Fifty-three patients had ORN in the mandible (85%) compared with nine in the maxilla (15%), and external beam was the most common mode of delivery of radiation (n=49, 79%). Interestingly most cases of ORN (n=37, 60%) occurred spontaneously without an inductive event such as tooth extraction (Table 1). In the study group, 30 patients (48%) had been given a combination of chemotherapy and radiotherapy as treatment for their primary tumour.

Table 1
Causes of osteoradionecrosis (ORN) depending on technique of irradiation.

| | External beam (n=49) | Intensity modulated (n=13) |
|---|---|---|
| Cause of ORN: | | |
| Induced | 23 | 2 |
| Spontaneous | 26 | 11 |
| Additional chemotherapy | 23 | 7 |

All patients were treated with pentoxifylline and tocopherol, either alone or supplemented with interventions such as antibiotics or resection (predominantly local debridement) depending on the clinical findings and the severity of the necrosis. Success was defined as the establishment of mucosal coverage at the sites of previously-exposed bone with symptomatic relief. According to these criteria 28 patients (45%) responded to pentoxifylline and tocopherol (Table 2) and five (15%) of the 34 non-responsive patients continued to have exposed bone, but reported that their symptoms improved with long-term treatment with pentoxifylline and tocopherol.

Of the 34 patients whose ORN failed to heal, half had died by the time that we collected the data. Of the 17 who remained ORN had progressed in 11, but not in four. Two were lost to follow up.

When pentoxifylline and tocopherol were used alone the mean duration of time to healing was 8 (range 2–24) months, while in those in whom ORN did not heal it was 13 (range 2–36) months. When the two drugs were used to supplement local surgical debridement, they were started a mean of 2 (range 0–5) months preoperatively and continued for 7 (range 1–9) months postoperatively in successful cases. Where ORN failed to resolve, preoperative and postoperative times were 4 (range 1–9) months and 19 (range 0–21) months, respectively.

Table 2
Management protocols according to severity of osteoradionecrosis (Notani Grade I-III).

| Management | Grade I | Grade II | Grade III | Total |
|---|---|---|---|---|
| Pentoxifylline and vitamin E only: | | | | |
| No. treated | 18 | 4 | 3 | 25 |
| No. resolved | 11 | 1 | 2 | 14 |
| Pentoxifylline, vitamin E, and antibiotics: | | | | |
| No. treated | 11 | 3 | 8 | 22 |
| No. resolved | 3 | 1 | 2 | 6 |
| Pentoxifylline, vitamin E, and debridement | | | | |
| No. treated | 2 | 7 | 1 | 10 |
| No. resolved | 0 | 5 | 1 | 6 |
| Pentoxifylline, vitamin E, and resection | | | | |
| No. treated | 0 | 0 | 3 | 3 |
| No. resolved | 0 | 0 | 2 | 2 |
| Pentoxifylline, vitamin E, and hyperbaric oxygen: | | | | |
| No. treated | 0 | 0 | 2 | 2 |
| No. resolved | 0 | 0 | 0 | 0 |
| Total: | | | | |
| No. treated | 31 | 14 | 17 | 62 |
| No. resolved | 14 | 7 | 7 | 28 |