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Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience

N.M.H. Mcleod [a,*], C.A. Pratt [b], T.K. Mellor [a], P.A. Brennan [a]

[a] *Department of Oral & Maxillofacial Surgery, Queen Alexandra Hospital, Portsmouth PO6 3LY, United Kingdom*
[b] *Maxillofacial Unit, St Rishards Hospital, Spitalfield Lane, Chichester PO19 6SE, United Kingdom*

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Abstract

Osteoradionecrosis of the jaw remains the most problematic consequence of radiotherapy for the management of head and neck cancer. Treatment is often complex and multimodal. New theories on its pathophysiology have allowed the development of potential treatment modalities, including the use of pentoxifylline and tocopherol. In this retrospective case series we examined the outcomes of patients with ORN prescribed pentoxifylline and tocopherol.

Keywords: Pentoxifylline, Tocopherol, Osteoradionecrosis, Jaw

Introduction

Osteoradionecrosis is a well recognised complication of radiotherapy for the treatment of cancer of the head and neck, and is reported to occur in up to 20% of patients.[1] It may arise spontaneously, but does so most commonly after trauma to the oral mucosa—for example, after dental extractions or through wearing ill-fitting dentures, and may present within weeks or many years after radiotherapy has been completed.

Recent developments have helped to clarify the pathophysiological processes involved and have led to new therapeutic avenues being explored.[2,3] Since Dion et al.[4] reported a reduced incidence of skin and soft tissue toxicity to radiotherapy in mice treated with pentoxifylline, several clinical trials have reported the benefits of pentoxifylline combined with tocopherol in the management of patients with osteoradionecrosis, with very promising results.[3–9]

Pentoxifylline inhibits tumour necrosis factor alpha (TNF-alpha), and tocopherol is a scavenger of reactive oxygen species which, in combination, have shown a positive synergistic effect on the progression of osteoradionecrosis.

We therefore adopted this treatment for all patients who presented to our unit with osteoradionecrosis after radiotherapy for the treatment of cancer of the head and neck. We review our clinical outcomes and compare them with existing reports.

Method

At clinical review in either the head and neck cancer multidisciplinary clinic or general oral and maxillofacial surgery clinics we identified patients with osteoradionecrosis who had been started on pentoxifylline and tocopherol since 2007, and reviewed their notes.

Treatment always consisted of pentoxifylline 400 mg twice daily and tocopherol 1000 IU once a day.

Clinical details recorded included the date, site, and stage of the primary tumour, and the treatment given, and any subsequent primary or recurrent cancer in the head and neck and its treatment. The date when osteoradionecrosis had been diagnosed, any preceding factors, and treatment given either

* Corresponding author. Tel.: +44 0 2392286099.
E-mail address: niall_mcleod@yahoo.co.uk (N.M.H. Mcleod).

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Table 1
Epstein staging of osteoradionecrosis.[10]

Stage	
I	Resolved
Ia	No pathological fracture
Ib	Pathological fracture
II	Chronic, non-progressive disease
IIa	No pathological fracture
IIb	Pathological fracture
III	Active, progressive disease
IIIa	No pathological fracture
IIIb	Pathological fracture

Table 2
Subjective objective management analytic (SOMA) scoring system for osteoradionecrosis.[11]

Score	
1	Minor symptoms. No treatment
2	Moderate symptoms. Conservative treatment
3	Severe symptoms affecting daily living. Aggressive treatment
4	Irreversible functional damage. Major intervention

Total SOMA score made from addition of the score of 4 individual elements.

before of after commencing pentoxifylline and tocopherol were also recorded.

Osteoradionecrosis was staged using the Epstein system (Table 1) and a subjective objective management analytic (SOMA) score (Table 2) was calculated at the commencement of the regimen and at the last review.[10,11] These assessments were the same as those used by Delanian et al.[8] and were used to allow for a direct comparison of results.

Results

Twelve patients were identified within the specified period (3 women and 9 men, age range 54–75 years). Details are given in Table 3. One patient had to stop treatment because of the side effects of pentoxifylline; three reported difficulty in swallowing the large tablet and resorted to crushing it despite it being contrary to pharmaceutical advice because of the enteric coating.

Table 4
Initial and final Epstein stage and SOMA score of study patients.

Case no.	Epstein stage		SOMA score	
	Initial	Final	Initial	Final
1	IIa	IIIb	8	13
2	IIIb	IIb	14	8
3	IIa	IIa	11	8
4	IIa	IIa	9	8
5	IIIa	IIIb	9	13
6	IIIb	Ia[a]	12	11[a]
7	IIIa	IIa	11	9
8	IIIa	Ia[a]	14	8[a]
9	IIa	IIa	8	8
10	IIa	IIa	9	7
11	IIIa	IIa[a]	9	8[a]
12	IIa	IIa	11	11

[a] Patients whose final score improved after operation despite progression of osteoradionecrosis while on pentoxifylline and tocopherol.

The Epstein stage and SOMA score at the beginning of treatment and at final review are given in Table 4. The Epstein stage had improved in five patients, was unchanged in five, and had become worse in two. The SOMA score had improved in eight patients, was unchanged in two, and had became worse in two. Although the final Epstein stage and SOMA score showed much improvement in cases 6, 8, and 11, their clinical stage worsened to Epstein stage IIIb for which they underwent radical resection and reconstruction after which they improved.

Discussion

Since its description in the 1920s, osteoradionecrosis of the jaws has posed a difficult problem for physicians. Early the-

Table 3
Characteristics of patients.

Case no.	Age (years)	Primary site	Primary treatment	Time from radiotherapy to osteoradionecrosis (months)	Precipitating factors	Duration of treatment (months)
1	68	Tongue base	Chemotherapy and radiotherapy	36	Dental extraction	28
2	66	Oropharynx	Chemotherapy and radiotherapy	8	Dental extraction	9
3	58	Oropharynx	MRND with postoperative radiotherapy	5	Dental extraction	8
4	60	Oropharynx	Chemotherapy and radiotherapy	69	Dental extraction	13
5	70	Oropharynx	Chemotherapy and radiotherapy	15	Dental extraction	7
6	70	Tongue base	MRND with postoperative radiotherapy	12	Unknown	14
7	59	Floor of mouth	Operation and postoperative radiotherapy	60	Unknown	6
8	54	Tongue	Radiotherapy	45	Dental extraction	46
9	71	Tongue base	Chemotherapy and radiotherapy	75	Dental extraction	4
10	63	Cheek	Operation and postoperative radiotherapy	7	Unknown	14
11	68	Oropharynx	Chemotherapy and radiotherapy	26	Dental extraction	24
12	75	Oropharynx	Operation and postoperative radiotherapy	72	Unknown	4[a]

MRND, modified radical neck dissection.
[a] Patient stopped treatment because of side effects.

ories about its pathophysiology including radiation, trauma, and infection, and the widely recognised theory of hypoxia, hypovascularity, and hypocellularity, have guided developments in treatment.[2] The mainstays of treatment, minimal surgical intervention where possible, and radical intervention by complete excision of the affected area with or without reconstruction where indicated, do little to alter the course of the disease itself. The use of hyperbaric oxygen remains controversial with few able to reproduce the early promising results reported by Marx.[12–14]

More recent developments in the elucidation of the pathophysiology of lesions in osteoradionecrosis have focused on the presence of radiation-induced fibrosis, and suggest that the key event in the development and progression of the condition is the dysregulation of fibroblastic activity in the irradiated area, which produces atrophic tissue with damage to microvessels, and allows increased leakage of inflammatory mediators. The presence of inflammatory mediators such as TNF-alpha, platelet-derived growth factor, fibroblast growth factors, and reactive oxygen species, in the irradiated tissue then triggers a further inflammatory response with increasing damage to local tissue. This increased inflammatory reponse can be triggered many years after intial radiotherapy.

Pentoxifylline is a methylated xanthine derivative that was marketed initially for the management of vascular disorders such as intermittent claudication, but has been found to act against some inflammatory mediators including TNF-alpha. Tocopherol is a methylated phenol compound with *Vitamin E* activity and is a scavenger of reactive oxygen species. These two drugs in combination have shown a positive synergistic effect on the progression of fibrotic and inflammatory lesions that arise from radiotherapy treatment, most noticeably in the study by Delanian et al. where the lesions in all 18 patients showed considerable improvement, and 16 resolved completely.[8] A more recent trial by the same group has shown similarly encouraging results.[9] We could not identify any other studies using a similar regimen of pentoxifylline and tocopherol in the management of damage from radiotherapy in the head and neck.

Our results in Portsmouth are much poorer than those produced in Paris, and the reasons for this are not immediately apparent. Certainly, the patients were comparable in terms of Epstein staging and SOMA score at the commencement of treatment, and although details of additional treatments used are lacking, there is no evidence of important differences, as all the patients were otherwise treated using similar principles.

The most obvious difference in approach is that the Paris group added clodronate, a non-nitrogen containing bisphosphonate drug, to the treatment regimen in patients who had not improved sufficiently at three months in the original trial, and from the beginning in the second trial.[8,9] We have been reluctant to introduce this to our protocol because of our experience with bisphosphonate-associated osteonecrosis of the jaws which makes the addition of a drug that can induce osteonecrosis to the treatment of patients who already have the condition somewhat counter-intuitive.[15] There is, however, little evidence for the development of bisphosphonate-associated osteonecrosis with clodronate, and it has been used as a substitute bisphosphonate in patients with bisphosphonate-associated osteonecrosis who are not able to stop their bisphosphonate treatment completely.[16] Its action in preventing further osteolysis while pentoxifylline and tocopherol reduce the inflammatory response does have some merit, and our current disappointing results with the use of pentoxifylline and tocopherol alone suggest that further studies are needed.

The use of pentoxifylline and tocopherol in the management of patients with osteoradionecrosis of the jaws cannot be supported on the basis of our current results, but acquisition of prospective data with a larger group would be prudent before such a promising treatment is abandoned. Clodronate may need to be added to the treatment regimen in cases of progressive osteoradionecrosis to gain maximum benefit.

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