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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

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Abstract

This study is a retrospective review of treatment outcomes of osteoradionecrosis (ORN) of the mandible with specific reference to the evolving role of medical management with pentoxifylline, tocopherol, and doxycycline. We reviewed the presentation and management of 71 patients treated for ORN of the mandible at the regional head and neck unit during a 15-year period to January 2011, and categorised them into three grades using the Notani classification: grade I ($n = 28$), grade II ($n = 16$), and grade III ($n = 27$). Twelve patients with grade I ORN, 3 with grade II, and 10 with grade III, were prescribed medical treatment. Of these, three with grade I, and two with grade II ORN were cured, and progression of the disease had halted and there was satisfactory control of symptoms in eight with grade I and four with grade III disease. Patients who failed to respond to conservative treatment were further analysed for the need for free flap reconstruction. Medical management was introduced as a standard treatment in January 2006. Of the 39 patients diagnosed before this, 20 (51%) required resection and free flap reconstruction compared with only 8/32 (25%) after it had been introduced.

Keywords: Osteoradionecrosis; Debridement; Hyperbaric oxygen therapy; Medical management; Survival

Introduction

Osteoradionecrosis (ORN) can occur at any time, but 70–94% of cases have been reported to develop within the first 3 years after radiotherapy.[1,2] The reported incidence of ORN of the mandible varies from 2.6% to 22%.[2–4] Established ORN has a varied presentation ranging from mild asymptomatic disease to severe pain, fistulas, suppuration, exposed bone, and pathological fracture. Conservative management has traditionally involved minimal surgical debridement and hyperbaric oxygen therapy (HBOT), but more recently, medical management with pentoxifylline, tocopherol and clodronate has been introduced. Patients with aggressive ORN often require radical resection and free flap reconstruction to achieve a satisfactory outcome.

HBOT is well known to have a positive influence the outcomes of operation by promoting angiogenesis in irradiated tissues,[5–7] but some authors have reported good outcomes without its use.[4,8] In a randomised controlled trial, Annane et al.[9] showed that HBOT is not better than placebo, and they raised concerns about its damaging effects. Given the equivocal evidence, there is a lack of enthusiasm among maxillofacial surgeons in the UK to prescribe it prophylactically or therapeutically.[10] Contemporary understanding of the pathophysiology of ORN based on the concept of radiation-induced fibrosis has allowed the introduction of new therapeutic regimens comprising pentoxifylline, tocopherol, and clodronate.[11–13]

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Table 1
Grades for osteoradionecrosis (ORN) based on Notani et al.[15]

Grade	Description
I	ORN confined to alveolar bone
II	ORN limited to the alveolar bone and/or mandible above the level of the inferior alveolar canal
III	ORN involving the mandible below the level of the inferior alveolar canal and/or skin fistula and/or pathological fracture

Until December 2005, at the regional head and neck unit in Liverpool, UK, it was not uncommon to refer patients with ORN for HBOT, and we have previously published their outcomes.[14] However, compliance with the treatment has always been a problem for some, and recently, because of this and the current understanding of the pathophysiology of the disease, treatment has tended to be medical. We therefore felt it timely to report the outcomes for patients who had medical treatment, and to make a valid comparison with those treated with HBOT. As in our previous study, patients were staged using the Notani classification.[14,15]

Method

We identified patients treated for ORN of the mandible from the regional head and neck oncology database, and cross-referenced data with their medical records. We divided them into three groups based on the Notani classification (Table 1).[15] After being monitored for a minimum of 3 months, patients with persistent and non-healing mucosal ulceration and exposure of mandibular bone in the absence of malignancy (confirmed histopathologically), were diagnosed with ORN. The main methods of treatment were minimal surgical debridement, HBOT, or medical management. Response to treatment was defined as complete healing, stable disease (symptoms controlled and the progression of disease halted), and progressive disease.

Medical treatment at our unit comprises pentoxifylline 400 mg twice daily, tocopherol 1000 IU/mg/day, and doxycycline 100 mg daily. This is continued long-term depending on side effects, progression of the disease, and symptoms.

Patients who did not respond to initial conservative treatment were further analysed for the need for free flap reconstruction and divided into two groups: those treated before January 2006 ($n = 39$) and those treated since then ($n = 32$). Information on those who had died was extracted from the case notes and from the Office for National Statistics. Follow-up was to 1 October 2011. Life-table estimates of survival with 95% confidence intervals (CI) were obtained for all patients and for time periods before and since 2006. The log-rank test was used to compare survival curves. Comparison between time periods for method of treatment, Notani grade, and outcome of initial conservative treatment, was done using the chi square test, and Fisher's exact test was used for free flap surgery. SPSS version 19 (IBM Corp) was used for all analyses apart from the life-table estimates with 95% CI, which were done with the help of Stata version 11.

Results

Seventy-one patients treated for ORN of the mandible from June 1995 to June 2011 were included in the study and followed up to October 2011 (median (IQR) 75 (41–119) months). Mean (IQR) age at the time of diagnosis was 62 (57–68) years, and 54 patients (76%) were male. The primary tumour sites were oral cavity ($n = 34$), oropharynx ($n = 32$), larynx ($n = 2$), parotid ($n = 2$), and occult ($n = 1$). Mucosal squamous cell carcinoma was the primary malignancy in all but two patients who had primary malignancy of the parotid gland. Median (IQR) total dose of radiotherapy was 64 (60–66) Gy (range 40–70) (data were available for 22/71 patients). A total of 33 patients had primary radiotherapy and 38 had adjuvant radiotherapy. The median (IQR) time from diagnosis of primary tumour to diagnosis of ORN was 25 (9–44) months (range 2–206). Life-table estimates of survival after diagnosis of ORN with 95% CI were 87% (76–93%) at 12 months, 74% (62–83%) at 24 months, and 60% (46–71%) at 60 months (Fig. 1). When patients were grouped according to the Notani classification, 28 had grade I ORN, 16 had grade II, and 27 had grade III.

Conservative management of ORN

Table 2 shows the results of conservative management. Twenty-eight patients had grade I ORN. Median (IQR) age at diagnosis was 61 (57–65) years (range 52–80). The median (IQR) time from diagnosis of primary tumour to diagnosis of ORN was 32 (12–73) months (range 6–206).

Sixteen patients had grade II ORN. Median (IQR) age at diagnosis was 64 (63–73) years (range 47–84) and median (IQR) time from diagnosis of primary tumour to diagnosis of ORN was 23 (12–35) months (range 4–117). The duration of medical treatment ranged from 9 to 11 months (Table 3). Both patients who healed after medical treatment had done so within 9 months of starting treatment.

Patients with grade III ORN were treated conservatively with the intention to stabilise the condition and control the symptoms, but not to cure. A total of 27 patients had grade III ORN. Median (IQR) age at diagnosis of ORN was 60 (53–67) years (range 39–77) and median (IQR) time from diagnosis of primary tumour to diagnosis of ORN was 22 (7–42) months (range 4–193).

Table 3 shows the duration of medical management and response to treatment.

Patients who required reconstruction with a free flap

Table 4 shows details of patients who required free flaps after conservative treatment had failed. Two patients with grade I ORN had reconstruction with a free flap, one at 4