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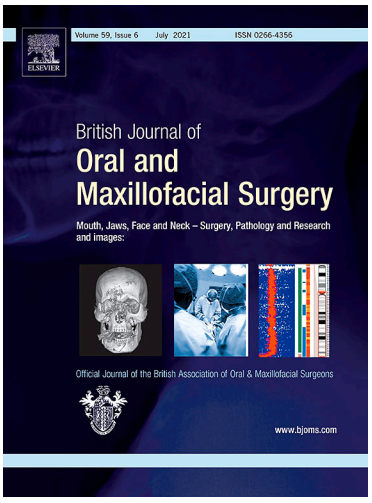

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Patients experience and perceived concerns regarding obtaining and taking prescriptions for head and neck osteoradionecrosis

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Keywords: patients experience; prescription; head and neck; osteoradionecrosis

Abstract

The main components of the medical management of osteoradionecrosis (ORN) are combinations of clodronate, pentoxifylline, tocopherol, sometimes with antibiotics or chlorhexidine rinses. Anecdotally in the Cheshire and Merseyside network, patients report having difficulties getting and taking their prescription, hence the aim was to survey patient experience of obtaining prescriptions, administration of the medications, and side effects. Patients prescribed tocopherol and pentoxifylline from the pharmacy department's record database from the period of January 2019 to June 2020 were invited to take part in a semi-structured telephone survey.

Sixteen patients out of a total 33 (48%) responded. 11 patients (69%) reported some issue collecting their repeat prescriptions, commonly low stock of medicines in community or unwillingness of GPs to prescribe. One patient permanently stopped treatment owing to difficulties obtaining medication, whilst for three there were temporary gaps in treatment. Difficulty in administration of the medications was reported in 7 patients (44%) patients, most commonly in those with pre-existing dysphagia. Issues related to difficulties in swallowing the large pentoxifylline tablet or with the vitamin E capsules. Patients crushed the medications, but this was associated with gastrointestinal side-effects in one patient who had to stop treatment. One patient stopped chlorhexidine mouthwash due to oral soreness.

In conclusion, medical management of ORN is well tolerated by patients. There is difficulty for patients getting prescriptions in primary care. Few patients need to stop taking the medication due to difficulty in administration or side-effects. More patient information would be useful for all concerned.

Keywords: patients experience; prescription; head and neck; osteoradionecrosis

Introduction

Osteoradionecrosis (ORN) of the jaws is a relatively uncommon complication after the delivery of radiotherapy for the treatment of head and neck cancer (HNC). The prevalence of which being between 5-15%, with the mandibular body being the commonest site affected following external beam radiotherapy (1). ORN can have a profound impact on health-related quality of life with issues often attributed to difficulties with trismus, pain, chewing, speaking, swallowing, and psychosocial wellbeing (2-4). Rates of ORN are likely to rise due to increasing incidence of oral and oropharyngeal cancer, frequent use of radiotherapy and chemoradiotherapy particularly in the Human Papilloma Virus positive groups (HPV), and growing numbers of long-term survivors (5, 6).

Recent considerations in the pathogenesis of ORN support the fibroatrophic theory (7, 8). This has resulted in recommendations regarding drug therapies including pentoxifylline, tocopherol (PENTO) with or without clodronate (PENTOCLO) used in combination (7, 9). At the Liverpool Head and Neck Centre, historically, 'quadruple therapy' has been prescribed – a combination of pentoxifylline, tocopherol, doxycycline, and chlorhexidine mouthwash. Recent reviews and a meta-analysis found over 60% of patients had significant improvement or resolution with the use of PENTO plus or minus clodronate (10, 11).

No life-threatening adverse reactions to various regimens using PENTO has been reported (7, 9, 12-14), however, there are reports of nausea, gastric irritation, malaise and lethargy, whilst rarely visual disturbance, diarrhoea, hallucinations, vertigo, nose bleeds, and insomnia, amongst other effects have been noted (9, 12, 15). Problems associated with the large tablet (pentoxifylline) requiring crushing to administer via gastrostomy has been reported and has also been noted to increase side effects (9, 16). One previous study (15) looked at the effect of a self-prepared liquid formulation of pentoxifylline on its tolerance profile, with over 11% reporting varying side effects (nausea, malaise, vomiting). Although evidence exists regarding side-effects, there is a lack on patient experience in terms of administration,

obtaining the prescriptions, use of 'quadruple therapy', and compliance with multiple medication in the setting of pre-existing functional difficulties, such as, pain and trismus (2, 3). Anecdotally, Nurse Specialists, Pharmacists, and clinicians at the Regional Centre have had feedback from patients regarding difficulties with their medical management, hence the aim of this study was to seek the patient experience in obtaining their prescriptions, difficulties in taking them and possible side effects, to help guide care.

Method

Thirty-three patients were identified from hospital pharmacy records having been prescribed either pentoxifylline or tocopherol from January 2019 to June 2020. Clinical and demographic patient data were collected from the hospital records system, notably age, gender, site of primary tumour, site of disease, duration from completion of radiotherapy to diagnosis, primary treatment modality, and dependence on enteral feeding devices. The severity of ORN was graded using Notani system (Grade I: confined to alveolar bone, Grade II: mandibular bone above the inferior alveolar canal, Grade III: below the inferior alveolar canal or demonstrating pathological fracture and/or skin fistula) (17).

A questionnaire was formulated with both categorical answers and free text sections covering a range of issues: drug combinations, side-effects experience, patients self-reported pre-existing dysphagia (resolved or continuing), dependence on enteral devices, modification of tablets, whether modification of drugs altered side-effects, whether prescriptions were collected in community or from the hospital, problems with obtaining medications, and whether patients stopped all or part of their treatment (from side-effects, problems with administration, or with obtaining medicines). The questionnaire was reviewed by members of the clinical team, pharmacy department and piloted with two patients.

Patients were initially invited to contribute via face-to-face surveying whilst attending for routine out-patient review however due to restrictions imposed during the coronavirus pandemic most surveys were performed over by telephone after providing written consent. The surveys were of a semi-structured nature. Audit approval was granted by the hospital Clinical and Audit Management System (No. 8062).

Results

Sixteen (48%) of the 33 patients contacted consented to be contacted via telephone and complete the survey. There was no obvious responder bias, patient characteristics are described in table 1. Common sites of primary tumour were tonsillar (14 patients, 42%) and base of tongue (7 patients, 21%). The mandibular body was the main focus of ORN (24 patients, 73%), with only one case reported in the maxilla. Nineteen (58%) of patients underwent surgery followed by post-operative radiotherapy and 13 (39%) received chemoradiotherapy. 28 (84%) were taking 'quadruple therapy'. Five patients (15%) were dependent on enteral feeding.

In respondents, 5 (31%) patients reported no difficulty obtaining their prescription. For 7 (44%) patients the GP refused to prescribe and for 4 (24%) there were problems with availability of medication at their local pharmacy (table 2). Vitamin E seemed to be the main difficulty either in terms of GP prescription or local pharmacy stock. The difficulties resulted in temporary pause in treatment for three patients and for one patient treatment was permanently discontinued (which was subsequently discontinued by the treating consultant). Ten (63%) patients collected all or part of their prescription from the hospital or have had to change from the local to hospital pharmacy during the course of treatment and for two patients the issue was exacerbated due to Covid-19 (one quoted his pharmacy as having stock

issues with vitamin E during the pandemic and the other had difficulties attending, even over phone, for medication review).

Seven (44%) patients reported pre-existing dysphagia, with three having ongoing difficulties (table 3). Two were feeding tube dependent and relied on crushing their medications. Problems in taking the medication was reported in 5 patients with pentoxifylline, 3 with vitamin E, 2 with doxycycline, and 1 with clodronate. Drug combinations were seen in 3 patients. Preparation modification occurred in 3 patients with medication being either crushed or prescribed in dispersible form.

Four patients experienced side-effects (table 4). Three were associated with pentoxifylline, of which two had gastric irritation and nausea and one a skin itching. Of the two with GI symptoms, one was mild enough for treatment to continue and in for the other, who was enteral device dependent, crushing tablets resulted in severe gastrointestinal reactions, including nausea, vomiting, and pain, and to the discontinuation of all treatment.
One patient reported an itching sensation which was not attributed to one medication, but they felt it was either pentoxifylline or vitamin E, they did not stop treatment. Another patient experienced burning sensation following the use of chlorhexidine mouthwash and they discontinued this medication only.

Discussion

Radiotherapy is commonly used in the management of HNC. As numbers of survivors increase there will be a rising number developing ORN. The medical management of ORN of the jaws is established but there is relatively little literature on patients experience of taking these medications. The findings from this survey can help provide better information and practical advice for patients, carers, and clinicians in primary and secondary care. The study used a semi-structured interview to gain information from patients through open questions and was piloted and refined using feedback from pharmacy staff and patients. There are several limitations, it reflects the experience of one cancer network which may not reflect others. The number of eligible patients and numbers responding to the survey are small, however it could be argued that, given the nature of an interview has provided representative and clinically meaningful findings. A larger scale audit, over multiple centres may help to understand better the scale and nature of problems facing patients.

The survey has identified difficulties in obtaining prescription in primary care. Pentoxifylline has been 'black-listed' in the regional formulary, recommended 'only in exceptional circumstances.' Whilst for vitamin E, the area prescribing committee do not list an indication for use. The status of these drugs in this region, compounded by a lack of knowledge of ORN by GP's might explain their unwillingness to prescribe repeat treatment. Training in oral cancer for GP trainees across the UK is limited (18), whilst medical students compared to their dental counterparts have less awareness around oral cancer (19). It is likely that knowledge of ORN will be even more limited. Cost was cited as a reason for GPs not to prescribe and prescribing budgets are under constant scrutiny. In the Cheshire and Merseyside cancer network, 100ml of liquid vitamin E is ~£70. This may help to explain some of the concerns regarding stock and repeat prescription.

Dysphagia has been self-reported in 59% of patients in receipt of head and neck radiotherapy, with 37% reporting severe dysphagia (20). Primary tumour sites in or adjacent to structures associated with swallowing can be impaired by late effects of radiotherapy and be negatively associated with development of dysphagia (21, 22). In this survey, tonsillar and base of tongue tumours accounted for a combined 64% of primary tumour sites. Patients with ORN report problems with pain, trismus, and swallowing (2, 3). In this survey, patients mentioned Speech and Language Therapists (SALT) having a positive intervention on their dysphagia. In order to improve compliance with treatment SALT input will be invaluable. Identifying patients who are experiencing some dysphagia prior to medical management may allow early SALT input. Pharmacists also have a role in giving advice regarding the prescription. Asking patients explicitly whether they experience trouble swallowing might not only influence the type of preparation but also be an opportunity to touch on possible side effects and measures that might be tried to obviate these.

Crushing medicines is commonly used in patients with dysphagia or dependent on enteral devices. Cleary (23), investigated the side effects of crushed pentoxifylline noting a dose dependent relationship, with higher doses of 600mg being more likely to cause worse reactions. Interestingly, out of the 3 patients who crushed medications only one sought advice prior to doing so. Dedicated head and neck pharmacists may be able to provide information for patients prior to starting therapy.

Patel (15), used pharmacy prepared liquid pentoxifylline for ORN patients with dysphagia, trismus, or enteral device dependency. They reported only 2 patients with gastric irritation, despite modification. Regarding our respondents, only one of those who crushed tablets reported severe gastrointestinal side effects (nausea and vomiting) from pentoxifylline, enough to discontinue treatment. 11.6% of patients in their study reported general side effects and in total 6 patients discontinued the medication (15). McLeod (16), reports 3 patients

modified pentoxifylline owing to its large size, as with two of the responders in this survey, their patients would also appear not to have sought advice.

Two of our patients reported gastric irritation (both due to pentoxifylline). Gastric side effects are relatively common, Delanian (9), reported 7.4% of patients experienced mild gastric irritation; whilst Dissard (24), found 11.1% of subjects experienced epigastralgia. A study into the management of radiation injury following breast cancer treatment found 21 patients experienced gastrointestinal side effects with PENTO compared to 5 in a placebo and tocopherol group (12). Further complaints from the use of PENTO, with or without clodronate include diarrhoea, nausea, vomiting, insomnia, vertigo, lethargy, headache, bruising, excess sweating, and hallucinations (9, 12, 15, 24).

Although commonly mild, side effects do lead to cessation of treatment. Patel (13), reported 4 patients who could not tolerate administration of pentoxifylline and a further 2 who could not tolerate tocopherol; whilst McCaul (14), report 2 out of 18 patients could not tolerate treatment. Compliance has previously been reported as nearly 90% with a PENTOCLO regime (24). Transient dose reductions and symptomatic management (for example, proton pump inhibitors, PPI) have been used to alleviate the impact of side effects (9, 12, 24) and may improve long-term compliance. Adherence with PENTO regimes following breast irradiation, was found to be poor, but significantly improved with the use of an anti-emetic, interestingly use of a PPI negatively impacted on compliance (25).

One patient attributed ‘itchiness’ to either pentoxifylline or vitamin E, the former may cause skin reactions (26), but for the latter, it does not appear on product specifications (27). This patient also took doxycycline as part of quadruple therapy, given doxycycline is known to cause skin reactions and photosensitivity (28), and patients may not be able to accurately identify causative drugs it is possible this side effect was related to doxycycline. Side effects

which could not be attributed to either pentoxifylline or vitamin E, including rash, alongside vomiting and nose bleeds, have been reported (15).

In conclusion, this study has highlighted the difficulties some patients experience in respect to their medication for ORN. Better coordination of prescribing services is essential. As a regional service, distance to obtain repeat prescription and the avoidance of clinic review, might mean that a central postal prescription service could be considered. In terms of side-effects, it would seem appropriate for some patients to have a gastrointestinal prophylaxis regime, whether this be antiemetic therapy or gastro-protectants. Transient dose reductions might have some benefit and can be built into the regime and advice given to patients at the start of and during their treatment. There is a role for enhanced multi-professional teamworking, including both SALT and pharmacy staff. These allied health professionals provide specific advice tailored to the complex needs of the individual. Development of a patient information leaflet based on the findings of this survey is ongoing.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement/confirmation of patient permission

Clinical Audit Management Services approved. Patient permission obtained

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Table 1: patient characteristics

	Responders	Non-responders	Total
Age			
Mean	65.38	61.35	63.30
Range	51-80	49-75	49-80
Gender			
Male	12	16	28
Female	4	1	5
Grade (Notani)			
I	3	6	9
II	3	4	7
III	10	6	16
N/A (Maxillary)	0	1	1
Combination of therapy*			
QT	13	15	28
TT	1	1	2
TT + Doxycycline	2	1	3
Site of Primary Tumour			
Tonsil	8	6	14
Base of Tongue	3	4	7
Floor of Mouth	1	2	3
Naso/oropharynx	2	0	2
Retromolar	1	1	2
Tongue	1	1	2
Maxilla	0	1	1
Unknown	0	2	2
Site of ORN			
Body	13	11	24
Parasymphysis	0	3	3
Maxilla	0	1	1
Symphysis	1	0	1
Bilateral Angle/Body	2	1	3
Bimaxillary	0	1	1
Modality of Primary Treatment			
Surgery & PORT	10	9	19
Chemoradiotherapy	5	8	13
Primary Radiotherapy	1	0	1
Completion of RTX to Diagnosis			
Median (IQR)	53 (24-105)	36 (12-84)	45 (20-96)
Range	5-214	3-165	3-214
Dependent on Enteral Feeding Device			
Yes	2	3	5
No	14	14	28

**QT = Quadruple therapy (Pentoxifylline, Tocopherol, Doxycycline, Chorhexidine); QT+ Amox/Met (quadruple therapy where doxycycline has been switched to amoxicillin and metronidazole for a period of their therapy); TT = triple therapy (Pentoxifylline, Tocopherol, Clondronate); TT + Doxycycline (triple therapy and concurrent use of doxycycline); PORT = post-operative radiotherapy*

Table 2: difficulties experienced obtaining medicines

Pt No.	Where they collected medicines?	Issues cited with obtaining prescriptions	Did collection issues lead to discontinuation of the treatment?	Patient comments?
1	Local and Hospital	GP would not prescribe	Yes – Temporary	The GP stopped prescribing Vitamin E, they had to subsequently collect prescriptions from the hospital causing a temporary halt in vitamin E treatment
2	Local	No issues	No	-
3	Hospital	Local stock issues	No	No availability of liquid vitamin E in community meant travel to hospital for prescriptions
4	Hospital	GP would not prescribe	No	-
5	Local and Hospital	GP would not prescribe	No	GP would not prescribe pentoxifylline or vitamin E
6	Hospital	GP would not prescribe	No	The cost was cited as a reason for the GP not to prescribe
7	Local	No issues	No	-
8	Local and Hospital	Local stock issues	Yes – Temporary	COVID-19 impacted on vitamin E stock in local pharmacies and prescription had to be temporarily collected from the hospital, this resulted in a gap in treatment
9	Local	No issues	No	-
10	Local	GP would not prescribe	Yes	GP stopped prescribing treatment for an unknown reason, prior to which there had been no issues obtaining repeat prescriptions, the patient permanently stopped treatment. It has since been discontinued by their treating consultant.
11	Hospital	GP would not prescribe	No	-
12	Hospital	No issues	No	-
13	Local	No issues	No	-
14	Local	GP would not prescribe	Yes – Temporary	In COVID-19 lockdown the GP requested a medicine review appointment, the patient could not attend face-to-face or e-consult, resulting in a four-month gap, now resolved
15	Local and Hospital	Local stock issues	No	GP has queried the prescription but still written it. Vitamin E stock low in community and so this was collected from the hospital
16	Hospital	Local stock issues	No	No local vitamin E stock resulted in collecting prescription from the hospital. On one occasion the hospital had low vitamin E stock and on a further occasion would not dispense without contacting the prescriber. They also received a postal prescription in COVID-19 lockdown which was very convenient

Table 3: Patients self-reporting pre-existing dysphagia

Pt No.	Problematic Medication	Status	Enteral Device	Tablet Modification	Advice prior to modification	Issues with modification	Comments
3	VE capsules	Resolved	No	No	-	-	Dysphagia improved with time. Previously only able to swallow VE liquid, now can swallow capsules
5	P Tablet	Ongoing	No	No	-	-	Ongoing difficulties swallowing pentoxifylline despite SALT input
7	P Tablet C Tablet	Ongoing	Yes	Yes – Crushed P and C. Used VE liquid	Sought advice from pharmacist	Severe GI irritation, vomiting	Was warned about potential effects of modification, had to stop treatment. No blocking of enteral tube
8	VE capsules	Resolved	No	No	-	-	Initially difficulty swallowing VE capsules, requiring liquid. Dysphagia improved with SALT input, can now manage VE capsules
11	P Tablet D Capsule	Resolved	No	Yes – Crushed P and dispersed D	Demonstrated on Ward	No	Tablet modification resolved issues with dysphagia
12	P Tablet	Resolved	No	No	-	-	Had trouble swallowing pentoxifylline since improved with SALT
14	P Tablet D Capsule VE Capsule	Ongoing	Yes	Yes – Crushed P and dispersed D and VE	Followed example set using other medicines	No	The patient experienced silent aspiration. Modification had no impact on side-effects, or blocking of enteral tube

SALT = speech and language therapy. VE = Vitamin E. P = pentoxifylline. C = clodronate. D = doxycycline

Table 4: patients experiencing side effects

Pt No.	Side Effect	Causative Medication (patient reported)	Combination Therapy	Treatment Duration	Formulations	Medicine Modification	Enteral Device	Persisted	Discontinuation with Treatment
3	Skin Reaction	P or VE	QT	Long-term	P – Tablet VE - capsule	No	No	Resolved	No
5	Nausea, GI irritation	P	QT	Long-term	P - Tablet	No	No	Resolved	No
6	Oral burning sensation	CHX	QT	Long-term	CHX - mouthwash	No	No	Persistent	Yes, CHX only
7	Nausea, Vomiting, GI irritation	P	TT	Short-term (<6 months)	P - Tablet	Yes - Crushed	Yes	Persistent	Yes, All treatment

P = pentoxifylline, VE = tocopherol, QT = quadruple therapy, TT = triple therapy, CHX – chlorhexidine mouthwash