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Phase III randomised trial

A randomised controlled trial of Caphosol mouthwash in management of radiation-induced mucositis in head and neck cancer

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ABSTRACT

Purpose: This phase III, non-blinded, parallel-group, randomised controlled study evaluated the efficacy of Caphosol mouthwash in the management of radiation-induced oral mucositis (OM) in patients with head and neck cancer (HNC) undergoing radical (chemo)radiotherapy.

Patients and methods: Eligible patients were randomised at 1:1 to Caphosol plus standard oral care (intervention) or standard oral care alone (control), stratified by radiotherapy technique and use of concomitant chemotherapy. Patients in the intervention arm used Caphosol for 7 weeks: 6 weeks during and 1-week post-radiotherapy. The primary endpoint was the incidence of severe OM (CTCAE $\geqslant$grade 3) during and up to week 8 post-radiotherapy. Secondary endpoints include pharyngeal mucositis, dysphagia, pain and quality of life.

Results: The intervention (n = 108) and control (n = 107) arms were well balanced in terms of patient demographics and treatment characteristics. Following exclusion of patients with missing data, 210 patients were available for analysis. The incidence of severe OM did not differ between the intervention and control arms (64.1% versus 65.4%, p = 0.839). Similarly, no significant benefit was observed for other secondary endpoints. Overall, compliance with the recommended frequency of Caphosol was low.

Conclusion: Caphosol did not reduce the incidence or duration of severe OM during and after radiotherapy in HNC.

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Radical radiotherapy with concomitant chemotherapy is the standard of care for treatment of locally advanced head and neck cancer (HNC). Despite advances in computational technology and innovations in radiotherapy planning, treatment-related acute toxicity remains considerable.

Oral mucositis (OM) is a well-recognised acute toxicity of head and neck radiotherapy. OM often causes pain and dysphagia, leading to weight loss and malnutrition [1]. More importantly, poorly managed OM may lead to treatment interruptions, which are detrimental to treatment outcome [2,3]. A systematic review of 33 studies demonstrated that 34% patients with HNC receiving radical radiotherapy will develop severe (grade 3 or more) OM and the risk increases further to 43% for those receiving concomitant chemotherapy [2]. Patients with cancers of oral cavity and oropharynx are at the highest risk, as well as those receiving altered fractionation regimens [4,5].

The process leading to the development of mucositis is complex. The sequence of biological events is initiated by the production of reactive oxygen species which cause DNA strand breaks [6]. These, in turn, not only cause clonogenic death of the basal stem cells, but also trigger the transduction pathways resulting in activation of several transcription factors that lead to expression of several pro-inflammatory cytokines [6]. Despite better understanding of these processes, the standard-of-care management in patients with radiation-induced mucositis has not changed for many years and this unpleasant condition continues to pose a therapeutic challenge.

Caphosol is an aqueous solution of concentrated calcium phosphate, which is licensed for use in conditions resulting in dryness of the mouth and throat. As its composition is similar to natural saliva, it is postulated that it could help to maintain healthy oral mucous membranes during treatment by modulating the inflammatory process and promoting tissue repair [7]. Whilst its effec-

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tiveness has been documented for patients with haematological malignancies undergoing high dose chemotherapy [7,8], the role of Caphosol in radiation-induced OM in HNC is less clear with conflicting results in the literature [9]. To date, most studies of Caphosol in HNC were retrospective and even if prospective, were single-arm.

Here, we report the result of the first prospective phase III randomised controlled trial on the efficacy of Caphosol mouthwash in the management of radiation-induced OM in HNC.

Materials and methods

Study design and participants

This was a single institution, phase III, non-blinded, randomised controlled trial conducted at the Royal Marsden Hospital between December 2011 and January 2015. This study received approvals from the local clinical research and research ethics committee (CCR3571, REC no. 11/EE/0044).

Eligible participants were patients with any histologically proven carcinoma of the head and neck (except thyroid and larynx), aged 18 years or above, receiving (chemo)radiotherapy in a radical setting with Karnofsky's performance status >70%. The use of induction chemotherapy was permitted. Exclusion criteria included inability to use mouthwash, any previous radiotherapy to the head and neck region and mucosal ulceration at baseline (either post-surgery or post-induction chemotherapy).

All patients were treated with conventional fractionation (5 fractions every week). Both 3D-conformal and intensity-modulated radiotherapy (IMRT) techniques were allowed. Radiotherapy dose-fractionation was delivered as per institutional protocol: for primary treatment, macroscopic and microscopic disease were treated with 65 Gy and 54 Gy in 30 fractions, respectively, whereas for adjuvant radiotherapy, the post-operative surgical bed was treated with 60 Gy in 30 fractions, provided that there was no residual macroscopic tumour. As a general rule, tumours at or approaching midline received bilateral neck irradiation. Radiation protocol violations, such as treatment breaks greater than 1 week and failure to complete treatment, were recorded.

Concomitant platinum-based chemotherapy or cetuximab was permissible in this study. Typical systemic therapy regimens included cisplatin 100 mg/m^2 or carboplatin AUC 5 on day 1 and 29 and cetuximab 400 mg/m^2 loading dose prior to radiotherapy with weekly maintenance dose 250 mg/m^2. The choice of systemic therapy was at the discretion of the attending physician.

Study end points

The primary efficacy measure for this study was the incidence of severe (grade 3 or more) OM during and eight weeks after completion of (chemo) radiotherapy. We hypothesised that the use of Caphosol would lead to reduced incidence of severe OM compared to standard oral care alone. Other secondary efficacy measures included: (a) the duration of severe OM; (b) the incidence and duration of severe pharyngeal mucositis (PM); (c) the incidence and duration of severe dysphagia; (d) the incidence and duration of severe radiation-induced pain; and (e) patients reported quality of life (QoL).

Randomisation and trial interventions

Prior to starting (chemo)radiotherapy, recruited patients were randomised (1:1) to the use of standard oral care regimen (control) or Caphosol plus standard oral care (intervention). Randomisation was performed by the Clinical Trials and Statistics Unit (CTSU) at The Institute of Cancer Research (ICR) using random permuted blocks method. Patients were stratified by radiotherapy technique (unilateral versus bilateral) and type of therapy (chemoradiotherapy versus radiotherapy only).

The patients in the intervention arm started using Caphosol from the first week of radiotherapy. Caphosol was used as a mouthwash 4 times a day but the frequency could be increased up to 10 times a day at the physician's or patient's discretion. Patients used Caphosol for a total duration of 7 weeks; 6 weeks during radiotherapy and 1 week after completion. Depending on the symptoms, patients had access to other symptom control measures available in the control arm. If patients did not tolerate Caphosol, it could be stopped immediately and the reasons for discontinuation were recorded.

Patients in the control arm received standard treatment for OM. At our institution, this included normal saline mouthwash at least 4 times a day, aspirin mouthwash 3 times a day and tooth brushing with fluoride toothpastes prescribed by a dental hygienist. All patients were prescribed analgesia according to the WHO analgesic ladder [10] and topical anaesthetics, such as lidocaine gel. Anti-fungal or anti-viral therapy was also prescribed when necessary.

Evaluation and data collection

All trial evaluation data were collected prospectively during clinic visits. Baseline assessments included head and neck examination, nutritional status, pain relief requirements, smoking status, alcohol and recreational drugs use. Patients were assessed on a weekly basis during and up to 4 weeks following completion of radiotherapy. The final assessment fell on week 8 post-radiotherapy.

The scoring of radiation-induced side effects was performed objectively by trained physicians according to the NCI Common Toxicity Criteria scoring system (CTCAE) version 4.0. QoL was assessed using the EORTC quality of life questionnaire, QLQ-C30 version 3.0 and QLQ-HN35 at the following time points: pre-radiotherapy, week 4 during radiotherapy, week 4 and 8 post-completion of radiotherapy.

Sample size

The primary objective of the study was to determine whether the difference in the rate of severe OM in the intervention and control groups was at least 20%. We assumed that the proportion of patients with severe OM would be 20% and 40% in the intervention and control groups, respectively. A two group chi-squared test with a 0.05 two-sided significance level had 90% power to detect the difference between a Group 1 proportion (intervention arm), $\pi 1$, of 0.20 and a Group 2 proportion (control arm), $\pi 2$, of 0.40 when the sample size in each group was 109. Therefore, the calculated sample size required to detect a difference of at least 20% in the proportion of severe OM between the two arms with 90% power was 218 patients.

Analytical statistics

The data were analysed using STATA statistical software (Version 13.1; StataCorp LP, Texas, USA). Descriptive statistics were used to summarise patient baseline characteristics. All quantitative data were reported as mean and standard deviation. If the data were not normally distributed, median was used together with interquartile range. Qualitative data were presented as number of observations and percentages. All missing data were recorded.

The primary analysis was performed based on treatment actually received ('as treated') and included all patients who received at least one week of Caphosol mouthwash treatment. Patients with