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Feature and review paper

Efficacy of a supersaturated calcium phosphate oral rinse for the prevention and treatment of oral mucositis in patients receiving high-dose cancer therapy: a review of current data

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Efficacy of a supersaturated calcium phosphate oral rinse for the prevention and treatment of oral mucositis in patients receiving high-dose cancer therapy: a review of current data

Oral mucositis (OM) is a painful and debilitating complication of cancer therapy that can adversely affect patients' treatment regimens and quality of life. It is also considered to be a substantial burden on the financial and human resources of health services. Despite progress in the understanding of the pathophysiology of OM and the number of new treatments that have been developed, there remains an unmet need for effective preventative measures in clinical practice. Literature on oral healthcare management in oncology patients suggests that a preventative approach consisting of a supersaturated Ca^{2+}/PO_4^{3-} oral rinse (Caphosol®) aimed at maintaining oral hygiene, moistening and lubricating the oral cavity, effectively reduces the incidence and severity of OM. This review looked at data from all known adult and paediatric studies investigating the use of Caphosol® in patients receiving high-dose cancer therapy in order to evaluate its efficacy for both the prevention and treatment of OM. Thirty studies were identified. The majority of these studies ($n = 24$) found Caphosol® to be efficacious at reducing the grade and/or duration, as well as pain associated with OM. Despite important limitations, these data warrant serious consideration for the inclusion of Caphosol® in regimens for preventing or reducing the debilitating effects of OM.

Keywords: mucositis, oral mucositis, chemotherapy, radiotherapy, calcium phosphate rinse, Caphosol.

INTRODUCTION

Oral mucositis (OM) is a painful and debilitating inflammatory complication that frequently affects patients receiving chemotherapy and/or radiotherapy; the pain and ulceration can adversely affect a patient's daily functioning, quality of life (QoL) and nutrition, and may lead to local and systemic infections (Pico *et al.* 1998; Cerchietti *et al.* 2002; Avritscher *et al.* 2004; Brown & Wingard 2004; Eilers & Epstein 2004; Sonis 2004b; Quinn *et al.* 2007; Stone *et al.* 2007). OM may also have a dose-limiting effect on cancer treatments, necessitating a reduction in dosage and/or delays or interruptions to treatment. Not only can OM negatively impact the morbidity and mortality of cancer patients, but it may also increase hospitalisation and treatment costs, putting increased pressure on healthcare resources (Pico *et al.* 1998; Cerchietti *et al.* 2002; Avritscher *et al.* 2004; Epstein & Schubert 2004; Sonis 2004b, 2009; Keefe 2006; Elting *et al.* 2007).

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The ultimate aim of any OM therapeutic strategy should be to try to prevent OM from occurring; however, where OM cannot be prevented, effective treatments should be used to reduce the symptoms (Quinn *et al*. 2007). If oral ulceration is minimised, pain, infection, requirement for total parenteral nutrition (TPN), length of hospitalisation, and health service resources could be reduced, while QoL could be improved (Sonis 2004b, 2009).

There are several products available for the treatment of OM but, to date, there are relatively few that are aimed at preventing OM from developing. Palifermin, a recombinant human keratinocyte growth factor is one such product, but it is an expensive option and is only recommended in the stem cell transplant setting (Keefe *et al*. 2007). Some OM treatments provide barriers that protect the oral mucosa from external damage while the OM resolves; others help maintain oral hygiene, moisten and lubricate the oral cavity, or offer anti-infective prophylaxis. The efficacy of all of these products is not well established and healthcare professionals may struggle to choose a product or a treatment regimen that will bring benefits to the patient and be cost-effective. This is also reflected by the work of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) who have been unable to make recommendations on some of these products due to a lack of robust clinical evidence (Keefe *et al*. 2007).

Recent UK guidelines on the prevention and treatment of OM, produced by a UK multidisciplinary expert group of cancer and palliative care specialists, suggest the use of a number of measures – including regular assessment, good oral hygiene, saline mouth rinses, cryotherapy, Caphosol® (EUSA Pharma, Langhorne, PA, USA), palifermin, mucosal protectants, low-level laser therapy, topical and systemic analgesia, and the prevention and treatment of oral infections – for patients at risk of mild, moderate or severe OM. For patients at risk of moderate to severe OM, the guidelines recommend the use of Caphosol® (a neutral supersaturated Ca^{2+}/PO_4^{3-} oral rinse), 4–10 times daily, from the first day of chemotherapy and/or radiotherapy (Quinn *et al*. 2012).

To date there have been two full-length peer-reviewed publications and numerous single-centre observational evaluations examining the efficacy of Caphosol® in the cancer care setting. A substantial body of this evidence has already been presented at international conferences. This review set out to collate and examine the data from all known studies investigating the use of Caphosol® in patients receiving anti-cancer therapy in order to further evaluate its efficacy for both the prevention and treatment of OM.

METHODOLOGY

The following electronic databases were searched for studies, papers, conference abstracts and posters investigating the efficacy of Caphosol® for the prevention or treatment of OM in patients undergoing cancer therapy: PubMed, Google Scholar, Stanford HighWire and the Cochrane library. A search for relevant conference abstracts and posters from international conferences, including the Multinational Association of Supportive Care in Cancer/International Society of Oral Cancer (MASCC/ISOO), the European Group for Blood and Marrow Transplantation (EBMT), the American Society for Radiation Oncology (ASTRO), the European Society for Radiotherapy and Oncology (ESTRO), the European Haematology Association (EHA), the American Society of Haematology (ASH) annual meetings and the Oral Complications of Emerging Cancer Therapies conference held in 2009, was undertaken. In addition, the author obtained all conference abstracts that had been supplied to EUSA Pharma by investigators (worldwide) who had conducted trials with Caphosol®. Search strings for the literature searches are listed in Table 1.

STUDY DETAILS

Inclusion and exclusion criteria

For inclusion in this review, studies had to be published in English between January 2003 and April 2012 and involve an evaluation of Caphosol® for the prevention or treatment of OM in patients with cancer. After elimination of duplicates, 83 unique hits from the literature searches and other sources described in the methodology were identified. Any study that did not involve an evaluation of Caphosol® for the prevention or treatment of OM in patients with cancer were considered to be out of the scope for this review, and these were excluded. Of the remaining 38 studies, two were excluded because they did not measure OM directly (instead adopting surrogate measures of OM, e.g. antifungal, antibacterial or antiviral prophylaxis use) (Yablonovich *et al*. 2010; Oh *et al*. 2011). Two studies were excluded because they assessed standardised oral care protocols in which the contribution of Caphosol® was unclear (Bhatt *et al*. 2010; Ng *et al*. 2011). Three studies were excluded because they did not report the incidence or severity of OM (Bechtel & Devine 2009; Papadakis 2011; Recchia *et al*. 2011). Finally, one study was excluded because the description of the experimental

Table 1. Search strings used for the online search

Search string	Database	Hits
('supersaturated calcium phosphate' OR 'caphosol') AND ('mucositis' OR 'stomatitis')	PubMed	3
('supersaturated calcium phosphate' OR 'caphosol') AND ('chemotherapy' OR 'stem cell transplantation' OR 'radiotherapy')	PubMed	2
('supersaturated calcium phosphate' OR 'caphosol') AND ('mucositis' OR 'stomatitis')	Google Scholar	68
('supersaturated calcium phosphate' OR 'caphosol') AND ('chemotherapy' OR 'stem cell transplantation' OR 'radiotherapy')	Google Scholar	67
('supersaturated calcium phosphate' OR 'caphosol') AND ('mucositis' OR 'stomatitis')	Stanford HighWire	10
('supersaturated calcium phosphate' OR 'caphosol') AND 'chemotherapy'	Stanford HighWire	6
('supersaturated calcium phosphate' OR caphosol) AND 'stem cell transplantation'	Stanford HighWire	6
('supersaturated calcium phosphate' OR caphosol) AND 'radiotherapy'	Stanford HighWire	4
('supersaturated calcium phosphate' OR caphosol) AND ('mucositis' OR 'stomatitis')	Cochrane library	3
('supersaturated calcium phosphate' OR 'caphosol') AND ('chemotherapy' OR 'stem cell transplantation' OR 'radiotherapy')	Cochrane library	2
Unique hits		**59**

design was not sufficient to interpret the results (Ilemová *et al*. 2010). The resultant 30 studies (26 adult and 4 paediatric) that met all inclusion criteria consisted of two full-length peer-reviewed articles and 28 published abstracts/conference presentations, evaluating a total of 1392 patients from a range of cancer specialist centres, of whom 890 received Caphosol®.

RESULTS

Patients enrolled in the studies included those with haematological malignancies undergoing autologous or allogeneic haematopoietic stem cell transplantation (HSCT) ($n = 754$), as well as patients with solid cancers, including head and neck cancers ($n = 638$).

Most studies had a single-centre design and compared patients receiving Caphosol® with randomised, matched or historic controls receiving standard therapy. The most common method of OM assessment was the 5-point WHO grading scale (World Health Organization 1979) ($n = 16$) but the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale (National Cancer Institute 2010) ($n = 4$), Radiation Therapy Oncology Group (RTOG) (Cox *et al*. 1995) ($n = 2$), Oral Mucositis Assessment Scale (OMAS) (Sonis *et al*. 1999) ($n = 2$), the Objective Mucositis Score (OMS) ($n = 1$), and the National Institute of Dental and Craniofacial Research (NIDCR) (Wolff *et al*. 1990) ($n = 1$) assessment scales were also used.

All studies are summarised in Table 2, those that included 30 or more patients ($n = 17$) are described below.

Prevention of OM and reduction of OM severity or duration

Twelve of the 17 studies with 30 or more patients directly compared Caphosol® with a control treatment. Nine of these reported that Caphosol® prevented the development of OM or reduced the severity of OM. The other five studies were non-comparative, and each reported a lower incidence and severity of OM than would be expected, given the incidence of OM reported in the literature in similar patient populations (Blijlevens *et al*. 2008). The largest full-length publication reporting a comparative study of Caphosol® for the prevention and treatment of OM was published by Papas and colleagues in 2003. This was a double-blind, prospective, randomised controlled trial that compared Caphosol® with fluoride treatment in 95 allogeneic and autologous HSCT patients receiving high-dose chemotherapy. Patients in the Caphosol® treatment arm experienced significantly fewer mean days of OM (3.72 vs. 7.22; $P < 0.001$) and ulceration (2.18 vs. 5.27; $P < 0.002$) than controls, and had a significantly lower peak level of OM (1.38 vs. 2.41 on the NIDCR scale; $P < 0.004$). The study also reported that 40% of patients in the Caphosol® arm had no OM compared with 19% in the control arm (significance level was not reported). Duration of OM was similar for allogeneic and autologous patients receiving Caphosol®, whereas in the control arm, OM duration was longer for allogeneic transplant patients than for those receiving autologous transplants (Papas *et al*. 2003).

Waśko-Grabowska *et al*. (2011), also evaluated Caphosol® in patients undergoing HSCT. This was a single-centre study that compared Caphosol® with standard treatment in 56 patients receiving high-dose melphalan (MEL 200) or BEAM (carmustine, etoposide, cytarabine, and melphalan) chemotherapy prior to autologous HSCT. None of the patients treated with Caphosol® in the BEAM group experienced severe OM (grade 3/4 on the WHO OM scale), 50% only had mild OM (grade 1/2), and 50% had no signs or symptoms at all. By contrast, all patients in the control arm had OM, with 60% experiencing mild signs and 40% having severe signs and

Table 2. Studies evaluating Caphosol for the prevention and treatment of oral mucositis (OM)

Study	Patients analysed	Study design	Intervention	Control	Main findings	Other findings
HSCT						
Ambard *et al.* (2011)	56 patients undergoing autologous or allogeneic HSCT receiving BEAM, cyclophosphamide with TBI, or melphalan.	Single-centre assessment of Caphosol® vs. matched controls.	Caphosol® from start of conditioning until the end of neutropenia (n = 28).*	Standard treatment (n = 28).	**OM free (WHO scale):** Caphosol®, 9 patients (32%); Control, 4 patients (14%). **OM incidence:** Caphosol®, 19 patients; Control, 24 patients (P = 0.227). **Severe OM (grade 3–4):** Caphosol®, 4 patients; Control, 10 patients (P = 0.227).	**Morphine analgesia:** Caphosol® 10 patients; Control, 13 patients (P = 0.549). **Mean duration of morphine use:** Caphosol®, 9.9 days; Control, 11.4 days (P = 0.088).
Barbosa *et al.* (2011)	16 patients undergoing peripheral HSCT receiving BuCy2 and PHP-ALO.	Single-centre retrospective, comparative study.	Caphosol® (protocol not specified) (n = 8).*	Standard protocol (n = 8).	**OM free (WHO scale):** Caphosol®, 45% of patients; Control, 55% of patients. **Grade 2 OM:** Caphosol®, 61% of patients; Control, 39% of patients. **Grade 3 OM:** Caphosol®, 79% of patients; Control, 21% of patients.	**Pain free (descriptive verbal scale):** Caphosol®, 48% of patients; Control, 52% of patients. **Grade 1 pain:** Caphosol®, 38% of patients; Control, 62% of patients. **Grade 2 pain:** Caphosol®, 78% of patients; Control, 22% of patients. **Grade 3 pain:** Caphosol®, 54% of patients; Control, 46% of patients. **Grade 4 pain:** No patients. **TPN requirement:** Caphosol®, 83% of patients; Control, 17% of patients. **Requirement for IV morphine:** Caphosol®, 57% of patients; Control, 43% of patients.
Cannas *et al.* (2009)	6 patients undergoing allogeneic HSCT receiving cyclophosphamide in combination with TBI.	Single-centre prospective observational study.	Caphosol® 4–10 × daily during conditioning period (one week), then alternated with standard rinses for 2 weeks (n = 6).*	–	**No OM (WHO scale):** 5 patients, none reported pain **Grade 2 OM:** 1 patient, VAS score = 4	**Treatment compliance:** 77% of treatment days with at least four rinses.
Dłużniewska *et al.* (2011)	86 patients undergoing autologous or allogeneic HSCT.	Single-centre assessment of Caphosol® vs. historic controls.	Caphosol® from start of conditioning until signs of engraftment. (n = 34).*	Standard treatment (n = 52).	**Severe OM (unspecified 5-point scale):** Caphosol®, 32% of patients; Control, 60% of patients (P = 0.013).	**Mean days of parenteral opioid use:** Caphosol®, 8.0; Control, 10.86 days (P = 0.12). **Mean days of TPN:** Caphosol®, 9.9; Control, 14.9 (P = 0.011). **Duration of hospital stay:** No difference between groups.
Felício *et al.* (2011)	20 patients undergoing autologous HSCT.	Single-centre prospective comparative study.	Caphosol® (protocol not specified) (n = 10)*	Standard treatment (n = 10).	**OM free (unspecified 5-point scale):** Caphosol®, 20% of patients; Control, no patients. **Grade 1 OM:** Caphosol®, 40% of patients; Control, no patients. **Grade 2 OM:** Caphosol®, 40% of patients; Control, 20% of patients. **Grade 3 OM:** Caphosol®, no patients; Control, 50% of patients. **Grade 4 OM:** Caphosol®, no patients; Control, 30% of patients.	**Pain free (unspecified scale):** Caphosol®, 20%; Control, no patients. **Grade 1 pain:** Caphosol®, 30%; Control, no patients. **Grades 2–4 pain:** No patients. **Grade 5 pain:** Caphosol®, 30%; Control, 10%. **Grade 6 pain:** Caphosol®, no patients; Control, 10%. **Grade 7 pain:** Caphosol®, no patients; Control, 20%. **Grade 8 pain:** Caphosol®, no patients; Control, 30%. **Grade 9 pain:** No patients. **Grade 10 pain:** Caphosol®, 20%; Control, 30%. **Requirement for IV morphine:** Caphosol®, 40%; Control, 100%.
Hawcutt *et al.* (2010)	19 paediatric oncology patients at high risk of OM.	Single-centre assessment of Caphosol® vs. historic controls.	Caphosol® for 27/45 chemotherapy cycles (n = 12).	No Caphosol® over 42 chemotherapy cycles (n = 7).	**OM (WHO scale):** In Caphosol®-group patients, 16 cycles of chemotherapy were affected – 7 cycles (26%) when Caphosol® was administered, 9 cycles (50%) when it was not; in control patients 14 cycles (33%) were affected.	Caphosol® was well-tolerated.

Jarfaut *et al.* (2011)	16 patients undergoing autologous HSCT receiving high-dose melphalan alone or with BEAM.	Single-centre prospective randomised comparative study.	Caphosol® 4 × daily following standard treatment, from the first day of conditioning until 21 days after transplant (n = 8).	Standard treatment: chlorhexidine mouthwash + fluconazole oral solution after each meal (n = 8).	**OM free (WHO scale):** Caphosol®, 4 patients; Control, 4 patients. **Grade 1 OM:** Caphosol®, 1 patient; Control, no patients. **Grade 2 OM:** Caphosol®, no patients; Control, 3 patients. **Grade 3 OM:** Caphosol®, 1 patient; Control, 1 patient. **Grade 4 OM:** Caphosol®, 2 patients; Control, no patients. **Overall severity of OM:** No statistically significant difference between the two groups (P = 0.25). **Duration of OM:** Caphosol®, 8.5 days; Control, 7 days (P = 0.70).	**Mean level of pain (11-point scale):** Caphosol®, 3.3; Control, 2.7 (P = 0.86). **Maximum level of pain (11-point scale):** Caphosol®, 4.75; Control, 5 (P = 0.73). **Opioid use among patients with OM:** Caphosol®, 3 patients; Control, 1 patient (P = 0.48). **Duration of morphine use:** Caphosol®, 7.3 days; Control, 8 days (P = 0.34).
Lalioui *et al.* (2012)	30 paediatric patients undergoing autologous HSCT receiving high-dose chemotherapy.	Single-centre prospective observational study.	Caphosol® 6 × daily from the first day of high-dose chemotherapy conditioning (n = 16).†	–	**Grade 3–4 OM (OMS scale):** Developed in 12 patients out of 26 that showed good compliance. **Grade 4 OM:** Developed in 2 patients that showed bad compliance.	Caphosol® was well-tolerated.
Markiewicz *et al.* (2010)	40 patients undergoing allogeneic HSCT receiving busulfan, treosulfan, or TBI.	Single-centre RCT.	Caphosol® 4 × daily from the first day of conditioning until reaching ANC 0.2 G/l (n = 20).*	Standard topical mouth treatment with salvia, antibacterial and antifungal solutions (n = 20).	**Mean oral toxicity (WHO scale):** Caphosol®, 0.9; Control, 1.8 (P = 0.02). **Duration of OM:** Caphosol®, 3.2 days; Control, 7.1 days (P = 0.02)	**Mean subjective peak pain in the mouth:** Caphosol®, 0.85; Control, 1.75 (P = 0.005). **Mean subjective pain intensity during OM period:** Lower in the Caphosol® than the control group (data not reported). **Intensity of swallowing problems:** Lower in the Caphosol® group than controls during the period when OM was experienced (NS). **Requirement for analgesia:** Caphosol®, 3 patients; Control, 9 patients **Duration of analgesia requirement:** Caphosol®, 1.1 days; Control, 3.4 days (P = 0.047). **Requirement for TPN:** Caphosol®, no patients; Control, 6 patients **Mean number of days of TPN:** Caphosol®, 0 days; Control, 1.9 days (P = 0.009).
Mourao *et al.* (2010)	20 HSCT patients undergoing autologous HSCT receiving BEAM.	Single-centre assessment of Caphosol® vs. matched controls.	Caphosol® from the first day of chemotherapy until cessation of symptoms (n = 10).*	No Caphosol® (n = 10).	**Severity of OM (WHO scale):** Lower in Caphosol®-treated patients than controls (data not reported). **Duration of OM:** shorter in Caphosol®-treated patients than controls (data not reported).	**Pain severity:** Lower in Caphosol®-treated patients than controls (data not reported). **Pain duration:** Shorter in Caphosol®-treated patients than controls (data not reported). **Requirement for morphine:** Lower in Caphosol®-treated patients than controls (data not reported). **Requirement for TPN:** Caphosol®-treated patients required no TPN vs. 5.4 days in control group. **Compliance with Caphosol® treatment:** 40% of patients rinsed 4 × daily; 55% rinsed 5 × daily.
Nguyen *et al.* (2010)	38 multiple myeloma patients undergoing autologous HSCT receiving MEL 200.	Single-centre retrospective audit of Caphosol® vs. matched controls.	Caphosol® 4–10 × daily from the first day of chemotherapy until resolution of OM or neutrophil count recovered (whichever was longer) (n = 27).	No Caphosol® (n = 11).	**No OM (WHO scale):** Caphosol®, 30%; Control, 0%. **Grade 1 OM:** Caphosol®, 33%; Control, 46%. **Grade 2 OM:** Caphosol®, 33%; Control, 36%. **Grade 3 OM:** Caphosol®, 4%; Control, 18%. **Grade 4 OM:** No patients.	**Requirement for opiate analgesics:** Caphosol®, 74% of patients; Control, 91% of patients (significance not reported). **Requirement for TPN:** None of the patients receiving Caphosol® required TPN. **Duration of hospital stay:** No difference between Caphosol® and controls.

Table 2. *Continued*

Study	Patients analysed	Study design	Intervention	Control	Main findings	Other findings
Papas *et al.* (2003)	95 patients undergoing autologous or allogeneic HSCT receiving TBI, melphalan, cyclophosphamide, VP16-BUC, or EPA/carboplatinum.	Double-blind randomised controlled trial.	Topical fluoride treatment followed by Caphosol® at least 4 × daily (n = 50).	Topical fluoride treatment followed by NaF 0.01% rinse at least 4 × daily (n = 45).	**Mean days of OM:** Caphosol®, 3.72; Control, 7.22 ($P < 0.001$). **Mean days of ulceration:** Caphosol®, 2.18; Control, 5.27 ($P < 0.002$). **Peak level of OM (NIDCR scale):** Caphosol®, 1.38; Control, 2.41 ($P < 0.004$). **No OM:** Caphosol®, 40% of patients; Control, 19% of patients (significance not reported).	**Mean peak level of pain (VAS):** Caphosol®, 19.80; Control, 50.33 ($P < 0.0001$). **Mean number of days of pain:** Caphosol®, 2.86; Control, 7.67 ($P < 0.0001$). **Duration of hospital stay:** No difference between Caphosol® and controls.
Pinto Marques and Branco (2011)	20 patients undergoing HSCT receiving chemotherapy.	Single-centre retrospective assessment of Caphosol® vs. controls.	Caphosol® 4–10 × daily after meals (n = 10).*	Na HCO_3 treatment 4–10 × daily after meals (n = 10).	**OM incidence:** Lower with Caphosol® than controls (data not reported). **OM severity (WHO scale):** Lower with Caphosol® than controls (data not reported).	**Requirement for analgesia:** Lower with Caphosol® than controls (data not reported). **Requirement for parenteral nutrition:** Lower with Caphosol® than controls (data not reported).
Pomper *et al.* (2011)	25 patients undergoing autologous or allogeneic HSCT receiving high-dose melphalan, Flu/Bu/ATG, Bu-Cy, BEAM or BEAC.	Single-centre prospective assessment of Caphosol® and Gelclair® vs. controls.	Standard rinse + Caphosol® (n = 10). Standard rinse + Gelclair® (n = 7).	Standard rinse (distilled water, chlorhexidine, bicarbonate powder) treatment (n = 8).	**OM incidence:** Caphosol®, 70% of patients; Gelclair®, 86% of patients; Controls, 100% of patients. **OM duration (mean days):** Caphosol®, 12.57; Gelclair®, 6.33; Controls, 9.88. **Mean OM intensity (WHO scale):** Caphosol®, 1.57; Gelclair®, 1.67; Controls, 2.00.	**Incidence of pain in oral cavity:** Caphosol®, 43% of patients; Gelclair®, 33% of patients; Controls, 75% of patients. **Use of opioid analgesia:** Caphosol®, 20% of patients; Gelclair®, 14% of patients; Controls, 50% of patients.
Potting *et al.* (2012)	154 patients undergoing autologous HSCT receiving high-dose melphalan.	Multi-centre prospective comparative study.	Caphosol® 4 × daily in addition to standard oral care for 21 days after the beginning of high-dose melphalan conditioning (n = 47).*†	Standard oral care (n = 107).	**Maximum mean OM grade (WHO scale):** Difference between groups not statistically significant. **Incidence of severe OM:** Caphosol®, 45% of patients (instead of the expected 65% observed in the POMA study (Blijlevens *et al.* 2008); Controls, not reported.	**Requirement for analgesia:** Significantly less for Caphosol®-treated patients than patients not treated with Caphosol®. **Requirement for antifungal medication:** Significantly less for Caphosol®-treated patients than patients not treated with Caphosol®. **Neutropenic fever:** Caphosol®, 53% of patients; Controls, 76% of patients (P = 0.0055).
Rzepecki *et al.* (2010)	44 patients undergoing autologous or allogeneic HSCT receiving BuCy, TBI/Cy, RIC, TBI/Flu, MEL 200, BEAM, TreoMel, or CarboVP16. Methotrexate and cyclosporin A were given for GvHD prophylaxis.	Single-centre observational study.	Caphosol® 4 × daily from the day before the beginning of chemotherapy until the end of hospitalisation (n = 44).*	–	**Severe OM (WHO scale):** No patients.	–
Skorobogatova *et al.* (2011)	5 paediatric patients undergoing allogeneic or autologous HSCT receiving high-dose chemotherapy.	Single-centre prospective observational study.	Caphosol® 4 × daily in addition to standard OM treatment (n = 5).*	–	**Amelioration of OM (OMAS):** Observed in children with severe OM (data not reported).	**Pain:** 4 patients experienced a decrease in pain. **Requirement for analgesia:** A progressive reduction of morphine doses was observed. **Adverse events:** None observed **Caphosol taste:** No aversions observed.
Somé *et al.* (2009)	8 patients (5 clinical haematology + 3 paediatric oncology) receiving chemotherapy for HSCT at high risk of OM.	Single-centre observational study.	Caphosol® 5 × daily (n = 8) with adjuvant fungicide (n = 3).	–	**OM free (unspecified 5-point scale):** 2 patients **Grade 3 OM:** 1 patient **Grade 4 OM:** No patients.	**Pain free:** 2 patients were pain free **Grade 2 pain:** 2 patients **Grade 3 pain:** 1 patient **Discontinuations due to aversion to the taste of Caphosol®:** 2 patients.

Waśko-Grabowska *et al.* (2011)	56 patients undergoing autologous HSCT receiving BEAM or MEL 200.	Single-centre assessment of Caphosol® vs. historic controls.	Caphosol® 4 × daily ($n = 32$). *†	No Caphosol® ($n = 24$).	**BEAM group** **Severe OM (WHO scale):** Caphosol®, no patients; 40% of control patients. **OM severity:** Difference in the severity distribution in favour of Caphosol® ($P < 0.05$). **Mean duration of mild OM:** Caphosol®, 2.25 days; Control, 8.6 days ($P < 0.001$). **MEL 200 group** **Incidence of grade 0 to 2 OM:** Caphosol®, 93%; Control; 93% ($P = 0.74$). **Incidence of grade 3 to 4 OM:** Caphosol®, 7.0%; Control, 6.6% ($P = 0.74$). **Mean duration of OM:** Caphosol®, 1.73 days; Control, 2.42 days ($P = 0.73$).	**BEAM group** **Requirement for opioid analgesics:** Caphosol®, 1 patient; Control arm, all patients. **MEL 200 group** **Requirement for opioid analgesics:** Caphosol®, 1 patient; Control arm, 1 patient. **Requirement for TPN:** Caphosol®, no patients.
Head and neck, and other solid cancers						
Feyer and Scholz (2009)	11 patients with head/neck tumours undergoing radiotherapy and/or chemotherapy.	Single-centre observational study.	Caphosol® 3–4 × daily for 5–12 weeks ($n = 11$).*†	–	**No OM (OMAS):** 1 patient **Grade 1–2 OM:** 7 patients **Grade 3 OM:** 3 patients **Grade 4 OM:** No patients.	Caphosol® was well-tolerated.
Godfrey and Cuccurullo (2010)	14 patients undergoing chemoradiotherapy for stage III–IVa oropharyngeal, laryngeal, nasopharyngeal, oral cavity cancers, and 2 patients with unknown primary cancer.	Single-centre observational study.	Caphosol® ($n = 16$) with adjuvant Gelclair ($n = 8$) or antifungal therapy ($n = 12$).	–	**Peak OM (NCI-CTC scale):** Group mean of 2.6.	**Requirement for analgesia:** 14 patients. **Requirement for feeding tube:** 11 patients. **Requirement for hospitalisation:** No patient during therapy. **Treatment compliance:** 15 patients fully compliant; 1 patient preferred 'magic mouthwash'.
Haas *et al.* (2008a)	218 patients undergoing chemotherapy, radiotherapy, or both for head/neck, lung, colon, breast cancer, other cancers, and lymphoma.	Analysis of data from an observational study.	Caphosol® 4–10 × daily ($n = 218$).†	–	Of the 170 patients completing follow-up, **Grade 0 OM (NCI-CTC scale):** 60% **Grade 1 OM:** 20% **Grade 2 OM:** 15% **Grade 3 OM:** 5% **Grade 4 OM:** 1%	**Requirement for pain medication:** 54% of patients received no pain medication; 25% received opioids; 21% received non-opioids (including NSAIDs). **Patient satisfaction with Caphosol®:** 76% of patients were 'satisfied' or 'very satisfied'. **Compliance**: 96% of days with one or more rinses; up to 90% of days with 2–6 rinses.
Haas *et al.* (2008b)	68 patients undergoing chemotherapy, radiotherapy, or both for head/neck cancer.	Sub-analysis of data from Haas *et al.* (2008a).	Caphosol® 4–10 × daily ($n = 68$).†	–	**Grade 0–1 OM (NCI-CTC scale):** 37–49% of patients **Grade 2 OM:** 33–39% of patients **Grade 3–4:** 18–23% of patients.	**Pain:** Grade ≤1, >40% of patients; Grade 2, 38% of patients; Grade 3: 18% of patients; Grade 4: No patients. **Requirement for opioid analgesia:** 54% and 64% of patients at weeks 3 and 8 of the study, respectively. **Dysphagia (NCI-CTC Dysphagia Scale):** No dysphagia, 18% of patients; Grade 1, 21% of patients; Grade 2, 36% of patients; Grade 3, 25% of patients; Grade 4, no patients. **Patient satisfaction:** 79% of patients were 'satisfied' or 'very satisfied'. **Compliance:** 96% of days with one or more rinses; 76% of days with 4 or more rinses.
Miyamoto *et al.* (2009)	42 head/neck cancer patients undergoing IMRT (some with adjuvant chemotherapy).	Single-centre assessment of Caphosol® vs. matched historic controls.	Caphosol® 4–10 × daily from the first day until the completion of treatment ($n = 21$).†	'Magic mouthwash', and salt and soda rinses ($n = 21$).	**Incidence of severe OM:** Lower in patients treated with Caphosol® than controls. **Severity of OM (WHO scale):** Lower in patients treated with Caphosol® than controls.	**Use of opioid analgesia:** Similar in Caphosol® and control groups. **Requirement for PEG:** Caphosol®, 33%; Controls, 57% (no significance value reported). **OM-related hospitalisation:** Caphosol®, 0% of patients; Control, 19% of patients.

Table 2. *Continued*

Study	Patients analysed	Study design	Intervention	Control	Main findings	Other findings
Nicolatou-Galitis *et al.* (2010)	19 head/neck cancer patients receiving radiotherapy with or without chemotherapy.	Single-centre assessment of Caphosol®.	Caphosol® from the initiation of radiotherapy (n = 3); during the course of radiotherapy after development of ulcerations (n = 16).*	–	**Severe OM (EORTC/RTOG scale):** 5 patients **Xerostomia:** 9 patients. **Symptom improvement at the end of therapy:** OM grade 3 to 2 – 3 patients; OM grade 2 to 1 – 1 patient; OM stable at grade 2 – 4 patients. **Symptom deterioration:** OM grade I to grade II – 1 patient.	**Pain (not graded):** 6 patients. **Requirement for antifungals:** 14 patients. **Requirement for antivirals:** 10 patients.
Pettit *et al.* (2011)	85 patients undergoing chemoradiotherapy for locally advanced squamous cell carcinoma of the head and neck.	Single-centre assessment of Caphosol® and MuGard™ vs. controls.	Caphosol® (n = 21), MuGard™ (n = 16). Regimen not specified.	Standard first line mouth care consisting of a 'cocktail' of aspirin, glycerine, sucralfate, and Gelclair® (n = 48). Regimen not specified.	**OM grade and duration (unspecified scale):** No significant difference between groups.	**Analgesia:** No evidence that either Caphosol® or MuGard™ improved analgesia score. **Nausea/dysphagia/rates of oral *Candida*:** No significant difference between groups.
Rao *et al.* (2011)	98 patients receiving head/neck radiation with or without cisplatin, carboplatin, or cetuximab.	Phase II multicentre assessment of Caphosol® vs. historic rare of OM.	Caphosol® 4–10 × daily from the first day until 8 weeks after completion of radiotherapy (n = 98).†	–	**Grade ≥2 OM (WHO scale):** all evaluable patients; the study failed to reject the null hypothesis that fewer than 90% of Caphosol®-treated patients would experience Grade ≥2 OM. **Symptom improvement:** 50% of patients between weeks 4 and 11 of study	–
Santos *et al.* (2010)	30 head/neck cancer patients receiving high-dose chemotherapy, radiotherapy, or both.	Single-centre observational study.	Caphosol® (n = 30).*	–	**Onset and severity of OM (NCI-CTC scale):** Caphosol® had a positive impact.	**Requirement for major opiates for OM-associated pain:** No patients. **Patient satisfaction:** High. **Treatment compliance:** High.
Stokman *et al.* (2010)	59 patients with oral or oropharyngeal malignancies receiving chemo/radiotherapy.	Single-centre assessment of Caphosol® vs. concurrent and historic controls.	Caphosol® 4 × daily (n = 27). *†	Standard treatment ($Na\ HCO_3$ rinse 8–10 × daily): concurrent (n = 16); historic (n = 16).	**Development and severity of OM (OMAS):** No significant difference between Caphosol® and concurrent controls (no data reported).	**Mouth and throat soreness (patient self-reported):** Non-statistically significant positive trend in favour of Caphosol® compared with historic controls (no data reported).
Thomson (2011)	60 patients undergoing whole mouth irradiation for oral and oropharynx cancers.	Single-centre assessment of Caphosol® vs. historic controls.	Caphosol® 4 × daily from the first day until completion of radiotherapy (n = 30).	Standard treatment (n = 30).	**Median grade of OM (CRC/EORTC/RTOG scale):** Significantly lower for Caphosol® than controls at weeks 3, 4, 5, 6 and 7 of the study (P = 0.004 for week 3, P = 0 for weeks 4, 5, 6 and 7).	**Requirement for analgesia:** A statistically significantly smaller amount of analgesia was required for patients receiving Caphosol® than those receiving standard treatment for weeks 4 to 7. **Oral intake of food:** significantly higher in Caphosol®-treated patients at weeks 3, 5, 6.

*Indicates support of the study/evaluation with Caphosol stock.
†Indicates some form of monetary funding to support the study/evaluation.
ANC, absolute neutrophil count; HSCT, haematopoietic stem cell transplantation; IV morphine, intravenous morphine; OMAS, Oral Mucositis Assessment Scale; PEG, percutaneous endoscopic gastrostomy; POMA, Prospective Oral Mucositis Audit; RCT, randomised control trial; TBI, total body irradiation; TPN, total parenteral nutrition; VAS, Visual Analogue Scale.

symptoms. The distribution of OM severities in the BEAM group was significantly different ($P < 0.05$) between the two treatment arms, in favour of Caphosol®. Additionally, patients treated with Caphosol® who did experience mild OM, had symptoms for a significantly shorter duration than patients in the control group who received standard treatment (2.25 vs. 8.6 days; $P < 0.001$). In the MEL 200 group, the incidence of grade 0 to 2 OM for both the Caphosol® and control arms was 93% ($P = 0.74$); incidence of grade 3 to 4 OM was 7% for both arms ($P = 0.74$); mean duration of OM in days was 1.73 and 2.42 days respectively ($P = 0.73$).

Dłużniewska *et al*. (2011) describe a single-centre study assessing the efficacy of Caphosol® in the management of OM following HSCT. This study prospectively assessed 34 HSCT patients (8 autologous and 26 allogeneic) who were treated with Caphosol® from the start of the conditioning regimen until signs of engraftment, and compared them with 52 historical controls (31 autologous and 21 allogeneic HSCT patients) who had not been treated with Caphosol®. The study found that a significantly lower proportion of patients in the Caphosol® group experienced severe OM (grade 3–4 on the WHO scale) than patients in the control group (32% vs. 60%; $P = 0.013$) (Dłużniewska *et al*. 2011).

Ambard *et al*. (2011) carried out a single-centre study comparing the efficacy of Caphosol® with standard care in 56 patients undergoing autologous or allogeneic HSCT receiving BEAM, cyclophosphamide with total body irradiation (TBI), or melphalan. Twenty-eight patients received Caphosol® from the start of conditioning until the end of neutropenia. Another 28 matched patients who did not receive Caphosol® served as controls. OM incidence was lower in patients receiving Caphosol® than controls (19 vs. 24 patients; $P = 0.227$), and fewer patients receiving Caphosol® than controls had grade 3–4 OM (WHO scale) (4 vs. 10 patients; $P = 0.227$) (Ambard *et al*. 2011).

Rzepecki *et al*. (2010) reported a single-centre assessment of the use of Caphosol® for the prevention of OM following HSCT. The study included 44 patients (12 receiving allogeneic and 32 receiving autologous transplantation) who were treated with Caphosol® (four times daily) starting on the day prior to commencing chemotherapy until the end of hospitalisation. Allogeneic HSCT patients received busulfan/cyclophosphamide, cyclophosphamide, fludarabine or reduced intensity conditioning chemotherapy regimens (with four patients receiving concomitant TBI); autologous HSCT patients received MEL 200, BEAM, treosulfan/melphalan, or carboplatin/etoposide chemotherapy. Granulocyte colony-stimulating factor was given to accelerate neutrophil engraftment and methotrexate and cyclosporin A to prevent graft-versus-host disease (GvHD). Although moderate to severe OM would be expected in this group of patients, the study reported no cases of severe OM (grade 3–4 on the WHO scale), while regimen-related mucositis manifested itself in the lower part of the alimentary canal in the form of diarrhoea, intestinal colic, nausea, and vomiting (Rzepecki *et al*. 2010).

Markiewicz *et al*. (2010) assessed the efficacy of Caphosol® vs. standard treatment in 40 patients undergoing allogeneic HSCT. Patients were stratified according to chemotherapy or radiotherapy regimen (busulfan, treosulfan or TBI), type of transplant (related or unrelated donors) and age prior to randomisation. The treatment group ($n = 20$) received Caphosol® four times daily starting from commencement of conditioning until an absolute neutrophil count (ANC) of 0.2 G/l, while the control group ($n = 20$) received standard topical mouth care, with salvia (plant extract), antibacterial and antifungal solutions. Mean grade of OM (measured on the WHO scale) was significantly lower in the Caphosol® group (0.9) than in the control group (1.8; $P = 0.02$). Duration of OM was also significantly shorter for Caphosol®-treated patients than for control patients (3.2 vs. 7.1 days; $P = 0.02$) (Markiewicz *et al*. 2010).

Nguyen *et al*. (2010) published a retrospective study that investigated the efficacy of Caphosol® in 38 patients with multiple myeloma (MM) receiving autologous HSCT with MEL 200 (27 treated with Caphosol® vs. 11 not treated with Caphosol®). OM was absent in just under one-third (30%) of patients treated with Caphosol®, while all those who did not receive Caphosol® had some level of the condition. Grade 3 OM was more common in the non-Caphosol® treated arm than the Caphosol®-treated arm (18% vs. 4%); no patients in either group experienced grade 4 OM (Nguyen *et al*. 2010).

A broader range of patients were included in an observational study by Haas and co-workers (2008a), which evaluated 218 cancer patients from an observational registry who received radiotherapy, chemotherapy or a combination of both, and were considered to be at high risk of developing OM. Patients in the registry had performed an oral rinse with Caphosol® 4–10 times daily. Results showed low incidence and severity of OM (graded using the NCI-CTC OM scale). Of the 170 patients who completed follow-up after receiving chemotherapy (cisplatin, carboplatin, oxaliplatin, docetaxel, paclitaxel, gemcitabine, capecitabine, doxorubicin, fluorouracil, cetuximab, cyclophosphamide, vincristine and others), radiotherapy, or both, 60% experienced no OM (grade 0), 20% had grade 1, and 15% grade 2 OM. Grade 3 or 4 OM was seen in only 5% and 1% of these patients respectively (Haas *et al*. 2008a).

A sub-analysis of the registry data, looking specifically at head and neck cancer patients (12% of whom received chemotherapy, 22% of whom received radiation therapy, and 66% of whom received combination therapy), also reported a low incidence and severity of OM: grade 0 or 1 OM was observed in 37–49% of patients; grade 2 in 33–39%; and grade 3 or 4 in 18–23% (Haas *et al*. 2008b).

In a study involving 60 patients undergoing whole mouth irradiation for oral and oropharynx cancers (30 patients receiving Caphosol® vs. 30 retrospective controls who received standard treatment with chlorhexidine), Thomson (2011) found that Caphosol® treatment was associated with significantly less severe OM than standard treatment, with a lower median OM grade (on the CTC/EORTC/RTOG assessment 5-point scale) at weeks 3 ($P = 0.004$), 4, 5, 6 and 7 ($P = 0.000$ for weeks 4, 5, 6 and 7).

A similar result was obtained by Miyamoto *et al*. (2009) who assessed the efficacy of Caphosol® in 42 head and neck cancer patients undergoing intensity-modulated radiation therapy (IMRT) (some with adjuvant chemotherapy). Twenty-one patients received Caphosol® 4–10 times daily from the first day until completion of treatment, while 21 matched historic control patients had received salt and soda rinses plus 'magic mouthwash' (one of numerous compounded topical solutions that included one or more of the following: anticholingeric agents, anaesthetics, oral antacids, oral protectants, sucralfate, and low doses of an opioid analgesic (Chan & Ignoffo 2005). Results showed a lower incidence of severe OM among patients treated with Caphosol® (Miyamoto *et al*. 2009). Likewise, Santos *et al*. (2010) carried out a single-centre observational study with 30 head and neck cancer patients receiving high-dose chemotherapy, radiotherapy or both and found Caphosol® to have had a positive impact on the onset and severity of OM.

In a multicentre study presented at the 2012 EMBT annual meeting, Potting *et al*. (2012) audited 154 patients undergoing autologous HSCT who received high-dose melphalan. Forty-seven patients who were administered a dose of 5.25 mg/kg of melphalan or higher received Caphosol® four times daily in addition to standard oral care for 21 days following the start of high-dose melphalan conditioning. The remaining 107 patients who received less than 5.25 mg/kg of melphalan received standard oral care. The incidence of severe OM in the high-dose melphalan group was only 45% compared with 65% incidence observed in a similar patient population in the European Prospective Oral Mucositis Audit (POMA) (Blijlevens *et al*. 2008; Potting *et al*. 2012). Moreover, there was no statistically significant difference in maximum mean OM grade (on the WHO scale) in the high-dose (with Caphosol®) vs. low-dose (without Caphosol®) melphalan group. The study also reported that a significantly smaller proportion of high-dose melphalan (Caphosol®-treated) patients suffered from neutropenic fever than those who received low-dose melphalan without Caphosol® (53% vs. 76%; $P = 0.0055$) (Potting *et al*. 2012).

Lalioui *et al*. (2012) presented data from a prospective observational study with 30 paediatric patients receiving high-dose chemotherapy in preparation for autologous HSCT. All patients received Caphosol® six times daily from the first day of high-dose chemotherapy conditioning. Two patients had to discontinue Caphosol® treatment because of vomiting. Twenty-six patients showed good compliance and grade 3–4 OM was only observed in 46% of these patients. The remaining two patients, who were poorly compliant with Caphosol®, developed grade 4 OM.

In addition to these results, findings from studies with fewer than 30 ($n = 13$) participants generally corroborated the efficacy of Caphosol® in lowering the incidence and/or severity of OM (Table 2): Ten of the 13 studies found Caphosol® prevented the development, or reduced the incidence and severity of OM; eight in patients undergoing HSCT (Cannas *et al*. 2009; Somé *et al*. 2009; Hawcutt *et al*. 2010; Mourao *et al*. 2010; Felício *et al*. 2011; Pinto Marques & Branco 2011; Pomper *et al*. 2011; Skorobogatova *et al*. 2011), and two in head and neck cancer patients (Feyer & Scholz 2009; Nicolatou-Galitis *et al*. 2010).

Three studies with more than 30 patients did not find a positive effect of Caphosol®. Rao *et al*. (2011) carried out a phase II multicentre trial investigating the efficacy of Caphosol® in 98 patients receiving radiotherapy for head and neck cancer. In addition to radiation therapy, 64% of patients had received cisplatin, 7% had received carboplatin, and 10% had received cetuximab. The primary endpoint of the study was the rate of functional mucositis (WHO grade ≥2), with the hypothesis that fewer than 75% of patients treated with Caphosol® would develop grade ≥2 OM. All evaluable patients in the study experienced grade ≥2 OM and thus the study concluded that Caphosol® did not prevent OM. Despite this result, between weeks 4 and 11 of the study, 50% of patients reported improved OM symptoms, which correlated highly with pain, swallowing and eating scores.

In a single-centre study to assess the efficacy of Caphosol® in patients with oral or oropharyngeal malignancies treated with chemoradiotherapy, Stokman *et al*. (2010) found no significant difference in development and severity of OM (measured on OMAS) between Caphosol®-treated patients ($n = 27$) and concurrent controls ($n = 16$)

who were treated with $NaHCO_3$ solution. Similarly, in a single-centre study assessing the efficacy of Caphosol® and MuGard™ against standard first-line mouth care consisting of a mixture of aspirin, glycerine, sucralfate, and Gelclair® (Helsinn Healthcare SA, Lugano, Switzerland), Pettit *et al*. failed to observe a significant difference in grade and duration of OM between three groups of head and neck cancer patients treated with Caphosol® ($n = 21$), MuGard™ ($n = 16$), or standard oral care ($n = 48$) (Pettit *et al*. 2011).

Reduction of pain associated with OM

Fourteen of the 17 studies with more than 30 patients reported an evaluation of OM pain (e.g. its prevention, reduction, or the use of analgesics associated with OM). All the comparative studies found that Caphosol® relieved or reduced OM-associated pain, and all the observational studies reported a low incidence and severity of OM-associated pain.

A significantly lower mean peak level of pain was reported for patients treated with Caphosol® than controls who received a fluoride rinse (19.80 vs. 50.33 on the Visual Analogue Scale (VAS); $P < 0.0001$) in the study carried out by Papas *et al*. (2003); Caphosol®-treated patients also experienced a lower mean number of days of pain than controls (2.86 vs. 7.67; $P < 0.0001$). The study by Markiewicz *et al*. (2010) showed that mean subjective peak pain [measured on a patient self-assessment scale graded from 0 (no pain) up to 10 (largest possible pain)] in the mouth were lower in the Caphosol® group than in patients receiving standard topical mouth care (0.85 vs. 1.75, respectively; $P = 0.005$) as was mean pain intensity throughout the duration of OM (data were not reported). The intensity of swallowing problems during the period when OM was experienced also tended to be lower with Caphosol® than patients in the control group.

The head and neck cancer subgroup analysis of Caphosol®-treated patients in the Haas registry revealed that over 40% had grade 1 pain or lower, while grades 2 and 3 pain on the NCI-CTC scale were experienced by 38% and 18% of patients, respectively; no grade 4 pain was reported (Haas *et al*. 2008b).

Requirement for analgesia was the most common method of pain evaluation. All studies that assessed pain in this way reported a reduced requirement for analgesia with Caphosol® relative to control groups (where used). In the Papas *et al*. study, patients treated with Caphosol® used a lower mean total amount of morphine during OM (34.54 mg vs. 122.78 mg; $P < 0.0001$) for a lower mean number of days (1.26 vs. 4.02; $P < 0.00015$) than those treated with the fluoride rinse. In the study by Waśko-Grabowska *et al*. (2011), only one Caphosol®-treated patient in the BEAM group required opioid analgesics, while all patients in the control arm required opioid analgesia; in the MEL 200 group, one patient from each treatment arm required opioid analgesics. Thomson (2011) also reported a reduced requirement for analgesia in radiotherapy patients receiving Caphosol® than those receiving standard treatment for OM at weeks 4, 5, 6 and 7 ($P = 0.000$ for week 4, $P = 0.001$ for week 5 and 6, $P = 0.003$ for week 7), and Nguyen *et al*. (2010) found that 74% of HSCT patients rinsing with Caphosol® required opiate analgesics compared with 91% of those who did not use Caphosol®. In patients receiving allogeneic HSCT, Markiewicz *et al*. (2010) found that analgesics were required in fewer patients for fewer days receiving Caphosol® than those receiving standard topical mouth care (3 and 9 patients, respectively) (1.1 vs. 3.4 days $P = 0.047$). Dłużniewska *et al*. (2011) found that the mean number of days of parenteral opioid use was 8.0 vs. 10.86 in the Caphosol® and control group respectively ($P = 0.12$). Ambard *et al*. (2011) reported that fewer patients treated with Caphosol® required morphine analgesia than controls (10 vs. 13 patients) and the Caphosol®-treated patients who did require it, did so for a shorter mean duration than controls (9.9 vs. 11.4 days). However, these results did not reach statistical significance ($P = 0.549$ and 0.088 respectively). Similarly, Potting *et al*. (2012) found that Caphosol®-treated patients required significantly less analgesia and antifungal medication than patients not receiving Caphosol® (data were not reported).

In the non-comparative study of Caphosol® by Haas *et al*. (2008a), 54% of patients required no pain medication, while opioids and non-opioids (including NSAIDs) were used by 25% and 21% of patients respectively. The sub-analysis of head and neck cancer patients from this study showed that opioid analgesia was required by 54% of patients at week 3 and 64% at week 8 of the study (Haas *et al*. 2008b). In the study by Santos *et al*. (2010), none of the head and neck cancer patients (all treated with Caphosol®) required major opiates for OM-associated pain. Conversely, Miyamoto *et al*. (2009) observed a similar opioid analgesia requirement in patients treated with Caphosol® and controls (48% vs. 52%; no significance level reported).

Six studies that had fewer than 30 participants produced similar findings in terms of amelioration of OM-associated pain and reduction in requirement for analgesia with Caphosol® use in patients undergoing HSCT (Somé *et al*. 2009; Mourao *et al*. 2010; Felício *et al*. 2011; Pinto Marques & Branco 2011; Pomper *et al*. 2011; Skorobogatova *et al*. 2011).

Two studies with more than 30 patients, however, did not find evidence that Caphosol® produced a benefit in terms of OM-associated pain. Although Stokman *et al*. (2010) found a positive trend in favour of Caphosol® in terms of mouth and throat soreness (via a patient self-reported measure) compared with a historical control group of patients who were not given Caphosol®, this was not statistically significant. Similarly, Pettit *et al*. (2011) found no evidence suggesting that Caphosol®-treated patients performed better on an analgesia score than patients treated with MuGard™ or standard oral care.

Effect on nutrition

Waśko-Grabowska *et al*. (2011), Nguyen *et al*. (2010), and Markiewicz *et al*. (2010) all reported that none of the patients receiving Caphosol® required TPN. Although in the Nguyen *et al*. (2010) study there was no difference in need for enteral feed between the two treatment groups, in the Markiewicz *et al*. (2010) study, there was a statistically significant difference between the Caphosol® and the control group in the mean number of days of TPN required (0 vs. 1.9 days; $P = 0.009$). Dłużniewska *et al*. (2011) also reported that patients in the Caphosol® group required a significantly smaller mean number of days of TPN than control patients (9.9 vs. 14.9; $P = 0.011$). Similarly, Miyamoto *et al*. (2009) found that fewer patients treated with Caphosol® than controls required percutaneous endoscopic gastrostomy (PEG) (33% vs. 57%; no significance level reported). Thomson (2011) made a similar observation, whereby oral intake of food was significantly higher in patients treated with Caphosol® than controls at weeks 3, 5, 6 ($P = 0.004$ for week 3, $P = 0.01$ for week 5, $P = 0.02$ for week 6). In the sub-analysis of head and neck cancer patients, Haas *et al*. (2008b) reported that 18% of patients did not experience any dysphagia while 21%, 36% and 25% of patients experienced grade 1, 2 and 3 dysphagia, respectively. Contrary to the findings reported in all of these studies, Pettit *et al*. (2011) found that there was no significant difference in the experience of nausea or dysphagia between patients treated with Caphosol®, MuGard™, or standard oral care. Data from two studies with fewer than 30 participants, also suggest that Caphosol®-treated patients required less TPN than patients not treated with Caphosol® (Mourao *et al*. 2010; Pinto Marques & Branco 2011).

Patient satisfaction

Four of the 17 studies with 30 patients or more reported data relating to the effect of Caphosol® on patient satisfaction. Data from the study by Haas *et al*. (2008a) suggest that Caphosol® is well-tolerated, with 76% of patients reporting being 'satisfied' or 'very satisfied'. Additionally, a high level of compliance was reported with 96% of days with one or more rinses and up to 90% of days with 2–6 rinses (Haas *et al*. 2008b). This was corroborated by Lalioui *et al*. (2012), who observed good compliance among 87% of the patients being assessed, as well as Santos *et al*. (2010) who reported that treatment compliance and patient satisfaction were high (no statistics reported). Similarly, seven studies with fewer than 30 participants, found that Caphosol® was well-tolerated, with little to no aversion to its taste being observed, even among paediatric patients (Cannas *et al*. 2009; Feyer & Scholz 2009; Somé *et al*. 2009; Godfrey & Cuccurullo 2010; Hawcutt *et al*. 2010; Mourao *et al*. 2010; Skorobogatova *et al*. 2011). One of two studies looking at treatment compliance, reported that patients used Caphosol® at least four times daily on 77% of treatment days (Cannas *et al*. 2009), while the other found that 95% of patients used Caphosol® at least four times daily (Mourao *et al*. 2010).

Duration of hospitalisation

Four of the 17 studies with 30 patients or more reported data relating to the effect of Caphosol® on duration of hospitalisation. Miyamoto *et al*. (2009) found that none of the Caphosol®-treated patients had OM-related hospitalisation compared with 19% in control group (no significance level reported). However, data from Papas *et al*. (2003), Nguyen *et al*. (2010) and Dłużniewska *et al*. (2011) indicate no differences in duration of hospital stay between patients treated with Caphosol® and those not. Data on the effect of requirement for hospitalisation from a study with fewer than 30 participants were in favour of Caphosol® (Godfrey & Cuccurullo 2010).

Potential cost savings

Two studies in this review reported data on the potential impact of Caphosol® on treatment cost. Using independent cost models reported in the literature, Miyamoto *et al*. (2009) estimated per patient incremental costs related to OM and calculated that Caphosol® could yield a potential cost saving of between US $1722 and $6917. Similarly, Dłużniewska *et al*. (2011) estimated that the reduction of five days of TPN requirement they observed in patients treated with Caphosol® compared with controls equated to a saving of €251 per patient in TPN costs.

DISCUSSION

Until recently, despite the recognition of the seriousness of OM in the cancer setting and the distress it can cause, much of the focus has been on treating the condition once the damage has occurred. However, with a greater understanding of the pathophysiology of OM, it is now easier to appreciate the damage caused to the oral cavity by cancer treatment, some of which may occur at a level that cannot be detected by gross medical examination (Sonis 2004a). Therefore, clinicians should endeavour to support patients in caring for their mouths, while employing appropriate preventative OM strategies, before any noticeable damage becomes apparent. Moreover, if OM does occur, effective treatments should be utilised to reduce the severity of OM and minimise the effect on the patient and their cancer therapy.

This review evaluated data from a variety of studies of heterogeneous design on the efficacy of Caphosol®, a supersaturated Ca^{2+}/PO_4^{3-} oral rinse, for the prevention and/or treatment of OM. The vast majority of the studies (24 out of 30) found Caphosol® to be beneficial for the prevention or treatment of OM in patients receiving high-dose chemotherapy and/or radiotherapy. In five comparative studies, including two full-length peer reviewed publications (Papas *et al*. 2003; Waśko-Grabowska *et al*. 2011), Caphosol® was associated with a statistically significant reduction in the severity of OM compared with control treatment with standard oral care (with or without 'magic mouthwash') or topical fluoride (Papas *et al*. 2003; Markiewicz *et al*. 2010; Dłużniewska *et al*. 2011; Thomson 2011; Waśko-Grabowska *et al*. 2011). In Waśko-Grabowska *et al*.'s study (2011) no patient undergoing BEAM treatment prior to HSCT who had received Caphosol® as a preventative measure, experienced severe mucositis however severe OM was reported in 40% of the control group. Papas *et al*. (2003) also saw a reduction in OM, with 40% of the control experiencing OM versus 19% experiencing OM in the Caphosol® treated group. Most other studies showed a lower incidence or severity of OM in Caphosol®-treated patients than controls but results did not reach statistical significance; in some cases OM was prevented completely. In one such study the results were surprising as severe OM would be expected in some patients receiving MEL 200 while undergoing autologous HSCT (Nguyen *et al*. 2010). Indeed, these positive findings were found despite the fact that many of the cytotoxic treatments received by the patients in the studies (i.e. high-dose chemotherapy, TBI, high-doses radiotherapy to the head and neck region, and treatments for GvHD prevention) are well known to be potentially toxic to the oral cavity. In particular, some studies included patients receiving a combination of chemotherapy and radiotherapy, in whom OM prevention can be very difficult to achieve.

Several of the studies included in the review were non-comparative studies; in these cases, it is pertinent to compare the reported rate of OM with the expected incidence for the given patient population. Most of the studies included patients receiving treatment for head and neck cancer, or autologous or allogeneic HSCT, where severe OM is expected to occur owing to the toxicity of the standard treatments. A good indicator of the expected OM incidence in the autologous transplant setting, and a robust comparator for these trial data, is the European POMA, which examined the incidence of OM in patients with either non-Hodgkin lymphoma (NHL) or MM. Severe OM (WHO grade 3 or 4 OM) occurred in 46% of patients with MM and 42% of patients with NHL, with a mean duration of 5.3 days and 5.5 days respectively (Blijlevens *et al*. 2008). Other studies have reported even higher incidences of OM. Grade 3 or 4 OM was observed in 67% of patients undergoing HSCT, and in 85% of patients receiving radiotherapy with or without chemotherapy for head and neck cancer (Wardley *et al*. 2000; Elting *et al*. 2005). Observational studies included in this review with high-risk populations such as these, suggest a preventative effect of Caphosol® as they generally report lower incidences of severe OM (grades 3–4) (1–27%) than would be expected.

Pain from OM is an important factor to consider when making treatment decisions, as its relief can potentially improve the QoL of adult and paediatric patients who may be dealing with numerous side effects of cancer therapy. In our review, studies that reported measures of OM pain prevention or reduction, or the use of analgesics associated with OM, gave results that were predominantly in favour of Caphosol®. Two studies reported statistically significantly greater reductions in pain intensity and duration in Caphosol®-treated patients than in non-Caphosol®-treated controls (Papas *et al*. 2003; Markiewicz *et al*. 2010). Papas *et al*. (2003) observed a significantly lower mean number of days of pain in the Caphosol®-treated group (2.86) compared with patients in the control group (7.67), a statistical difference of $P = 0.0001$, the study also noted that the dose of opiate required was lower in the Caphosol®-treated group. Two studies reported a reduced requirement for analgesia for OM-associated pain (Thomson 2011; Waśko-Grabowska *et al*. 2011). Waśko-Grabowska *et al*. (2011) observed that while only one patient treated with Caphosol® under the BEAM regimen required opiates for pain, 100% of those who underwent the same cytotoxic

regimen but who did not receive Caphosol® required opiates. Although none of the studies reported using a QoL assessment tool, one could surmise that any reduction in the severity and duration of OM and OM-associated pain, would lead to less distress and improved patient QoL, which are especially important for patients undergoing demanding treatments.

Nutrition is another factor that can be challenging for many adults and children with cancer, particularly for those undergoing HSCT or treatment for oral, or head and neck cancers. In studies reporting use of TPN, incidence of dysphagia, or PEG, favourable outcomes were achieved in patients treated with Caphosol®. In two studies, Caphosol®-treated patients were found to require significantly fewer days of TPN than patients not receiving Caphosol® (Markiewicz *et al*. 2010; Dłużniewska *et al*. 2011). In addition to these findings, a small number of studies reported data on compliance and found that few patients discontinued treatment, suggesting that Caphosol® was well-tolerated.

Beyond the clinical efficacy, it is important to consider the potential reduction in healthcare costs (length of hospitalisation, analgesia, and specialist care) that could be achieved by preventing or reducing the incidence and/or duration of OM, particularly in a time when cost-effectiveness has become a necessary aspect of health commissioning. Many studies covered in this review observed reductions in the required amount and duration of analgesia and TPN, with two studies reporting estimates of potential cost-savings with the use of Caphosol® (Miyamoto *et al*. 2009; Dłużniewska *et al*. 2011).

While the overall findings from these studies suggest that Caphosol® treatment was beneficial in preventing or reducing the severity and/or duration of OM, it is important to note that this review has a number of limitations. First, the study designs and patient populations were heterogeneous in nature and hence data could not be pooled or consolidated. Some of the studies evaluated were observational and, while data for similar groups of patients are available in previously published studies, one should be cautious when making cross-study comparisons. Most of the studies in this review involved only a single centre and therefore centre-specific treatment effects cannot be ruled out. Furthermore, as the majority of the studies identified were abstracts or conference proceedings, a detailed description of the study design, what constituted 'standard treatment', and detailed treatment protocols were often lacking. Moreover, many studies identified in the search did not have a sufficient number of patients to allow a meaningful interpretation of the results. In some studies, support was given by Pharma, in the majority of cases this involved free stock enabling the hospital to examine the possible benefits of Caphosol®. However, the company had no involvement in either the design or the implementation of these studies. In a comparison of the findings between studies that received support and those studies that received no support, no significant difference was found.

In conclusion, although OM continues to be a recognised side effect of cancer treatment in both the adult and paediatric settings, it no longer needs to be viewed as an inevitable consequence of treatment that cannot be prevented. The data from this review show that the inclusion of Caphosol® in OM-prevention and treatment regimens warrants serious consideration. Results from several ongoing prospective, randomised controlled studies should provide an improved evidence base for the use of Caphosol® within the cancer setting.

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REFERENCES

Ambard N., Brechard C., Noyel J., Gourioud M., Michallet A., Bouafia F., Broussais-Guillaumot F., Labussière-Wallet H., Coiffier B., Michallet M. & Petiot S. (2011) Prospective evaluation of supersaturated calcium phosphate oral rinse for oral mucositis after autologous and allogeneic stem cell transplantation. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Avritscher E.B.C., Cooksley C.D. & Elting L.S. (2004) Scope and epidemiology of cancer therapy-induced oral and gastrointestinal mucositis. *Seminars in Oncology Nursing* **20**, 3–10.

Barbosa I., Camboa T., Guedes C. & Ferreira M. (2011) Mucositis in patients undergoing allogeneic bone marrow: a comparative study between the protocol and established Caphosol®. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Bechtel T.P. & Devine S. (2009) Use of a calcium/phosphate oral rinse (Caphosol®) to lessen the mucositis following autologous peripheral blood stem cell transplantation. *Biology of Blood and Marrow Transplantation* **15**, 154.

Bhatt V., Vendrell N., Nau K., Crumb D. & Roy V. (2010) Implementation of a standardized protocol for prevention and management of oral mucositis in patients undergoing hematopoietic cell transplantation. *Journal of Oncology Pharmacy Practice* **16**, 195–204.

Blijlevens N., Schwenkglenks M., Bacon P., D'addio A., Einsele H., Maertens J., Niederwieser D., Rabitsch W., Roosaar A., Ruutu T., Schouten H., Stone R., Vokurka S., Quinn B. & McCann S.

(2008) Prospective oral mucositis audit: oral mucositis in patients receiving high-dose melphalan or BEAM conditioning chemotherapy – European Blood and Marrow Transplantation Mucositis Advisory Group. *Journal of Clinical Oncology* **26**, 1519–1525.

Brown C.G. & Wingard J. (2004) Clinical consequences of oral mucositis. *Seminars in Oncology Nursing* **20**, 16–21.

Cannas G., Thomas X., Chelghoum Y., Petiot S., Ducastelle S., Crocchiolo R., Brechard C., Nicolas E., Noyel J., Nicolini F., Paillet C. & Michallet M. (2009) Caphosol, an electrolytic mouth rinse solution, reduces the incidence of Oral Mucositis in allogenic bone marrow transplantation. A pilot study in Lyon. SFGM-TC.

Cerchietti L.C.A., Navigante A.H., Bonomi M.R., Zaderajko M.A., Menéndez P.R., Pogany C.E. & Roth B.M.C. (2002) Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* **95**, 2230–2236.

Chan A. & Ignoffo R.J. (2005) Survey of topical oral solutions for the treatment of chemo-induced oral mucositis. *Journal of Oncology Pharmacy Practice* **11**, 139–143.

Cox J.D., Stetz J. & Pajak T.F. (1995) Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *International Journal of Radiation Oncology, Biology, Physics* **31**, 1341–1346.

Dłużniewska A., Gozdzik J., Zygadlo D., Skoczen S., Krasowska-Kwiecien A., Czogala W. & Wiecha O. (2011) Supersaturated calcium phosphate rinse (Caphosol) in the management of mucositis after haematopoietic stem cell transplantation – single-centre experience. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Eilers J. & Epstein J.B. (2004) Assessment and measurement of oral mucositis. *Seminars in Oncology Nursing* **20**, 22–29.

Elting L., Cooksley C. & Garden A. (2005) *Clinical Outcomes of Radiotherapy-Induced Oral Mucositis Among Patients with Head and Neck Cancers*. 17th MASCC International Symposium. Geneva, Switzerland.

Elting L.S., Cooksley C.D., Chambers M.S. & Garden A.S. (2007) Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. *International Journal of Radiation Oncology, Biology, Physics* **68**, 1110–1120.

Epstein J.B. & Schubert M.M. (2004) Managing pain in mucositis. *Seminars in Oncology Nursing* **20**, 30–37.

Felício M., Santos A., Cerqueira I. & Duarte G. (2011) Comparative study of oral solutions in the prevention/treatment of mucositis. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Feyer P. & Scholz D. (2009) Clinical experience with supersaturated calcium phosphate solution (Caphosol®) for prophylaxis and treatment of oral mucositis in patients with head and neck tumours and undergoing radio and/or chemotherapy. 1st Annual ASORS Congress.

Godfrey L. & Cuccurullo C. (2010) Analysis of mucositis-associated health outcomes in patients treated with image-guided IMRT for head and neck cancer: should Caphosol be included in the MASCC/ISOO mucositis guidelines? *Supportive Care in Cancer* **18**, S108–S109; Abstract 08-064.

Haas M., Mercedes T. & Manyak M. (2008a) *Treatment of Oral Mucositis by Supersaturated Calcium Phosphate Oral Rinse in Patients Receiving Chemotherapy (CT) and Radiation (RT)*. American Society for Radiation Oncology 50th Conference. Conference Proceedings. Abstract 2530.

Haas M., Mercedes T. & Manyak M. (2008b) *Reduction of Painful Oral Mucositis by Supersaturated Calcium Phosphate Oral Rinse in Head and Neck Cancer Patients Receiving Chemotherapy and Radiation*. American Society for Radiation Oncology 50th Conference. Conference Proceedings. Abstract 2531.

Hawcutt D., Awogbem O., Bell E. & McDowell H. (2010) Mucositis prevention: Efficacy of Supersaturated Calcium and Phosphate solution (in high risk paediatric oncology patients. International Society of Paediatric Oncology SIOP XXXXII Congress.

Ilemová V., Silerová B., Murdychová E., Vackova B., Trnkova M. & Pohlreich D. (2010) Caphosol as a promising prophylaxis and treatment of mucositis during ASCT. 36th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Jarfaut A., Gairard-Dory A.C., Godet J., Bilger K., Berceanu A., Laplace A., Lioure B. & Gourieux B. (2011) Prospective evaluation of a supersaturated calcium phosphate mouth rinse for prevention of mucositis after high-dose chemotherapy and autologous haematopoietic stem cell transplantation. *European Journal of Hospital Pharmacy Practice* **6**, 48–51.

Keefe D.M., Schubert M.M., Elting L.S., Sonis S.T., Epstein J.B., Raber-Durlacher J.E., Migliorati C.A., McGuire D.B., Hutchins R.D. & Peterson D.E. (2007) Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* **109**, 820–831.

Keefe D.M.K. (2006) Mucositis management in patients with cancer. *Supportive Cancer Therapy* **3**, 154–157.

Lalioui S., Rodrigues S., Usubelli P., Valteau-Couanet D. & Dufour C. (2012) Evaluation of oral mucositis in children receiving supersatured calcium and phosphate solution during high-dose chemotherapy with autologous stem cell transplantation. 38th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Markiewicz M., Dzierzak Mietla M., Zielinska P., Kruzel T., Czerw T. & Kyrcz-Krzemien S. (2010) Caphosol mouth rinse diminishes oral mucositis in allo-HSCT recipients. ASH Annual Meeting and Exposition.

Miyamoto C., Wobb J., Micaily B., Li S. & Achary M. (2009) A retrospective match controlled study of supersaturated calcium phosphate oral rinse (SCPOR) vs. supportive care for radiation induced oral mucositis. International MASCC/ISOO symposium.

Mourao E., Correia A. & Pires R. (2010) Finally something good. 36th Annual Meeting of the European Group for Blood and Marrow Transplantation.

National Cancer Institute (2010) *Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [Online]*. National Cancer Institute, USA. Available at: http://ctep.cancer.gov

Ng V.C., Ong H.Y.P., Ng H.Y., Lim Y.J., Lim C.H., Hwang C.C.J., Lee M.L.E., Linn Y.C., Loh S.M.Y., Goh Y.T. & Hwang Y.K.W. (2011) Review of a standarized oral care protocol for patients undergoing hematopoietic stem cell transplantation. MASCC/ISOO.

Nguyen T., Dickson J., Kazi S., Oakervee H. & Nijjar R. (2010) Audit of the effectiveness of Caphosol mouthwash in Multiple Myeloma patients receiving Autologus Transplant with High Dose Melphalan at St Bartholomew's Hospital. BOPA.

Nicolatou-Galitis O., Sarri T., Kouloulias V., Dardoufas K., Sotiropoulou-Lontou A. & Kouvaris J. (2010) Efficacy and safety of Caphosol on an oral mucositis in head and neck cancer patients who received radiotherapy with or without chemotherapy. A pilot study. *Supportive Care in Cancer* **18**, S111–S112.

Oh J., Hong S.H., Yablonovich I., Donato M.L., Pecora A.L., Goldberg S.L., Vesole D.H., Siegel D.S., Feldman T., Goy A., Mato A.R., Richter J.R. & Rowley S.D.

(2011) Use of a super-saturated calcium phosphate mouth rinse for prevention and treatment of oral mucositis results in faster engraftment and hospital discharge than using a sodium bicarbonate rinse alone after autologous transplantation. *Blood* **118**. Abstract 4569.

Papadakis V. (2011) Caphosol mouth rinse application in infants and young children with oral mucositis. MASCC.

Papas A.S., Clark R.E., Martuscelli G., O'loughlin K.T., Johansen E. & Miller K.B. (2003) A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplantation* **31**, 705–712.

Pettit L., Davis G., Sanghera P., Whitmarsh S. & Hartley A. (2011) The use of MuGard™ and Caphosol® in patients with locally advanced squamous cell carcinoma of the head and neck. *Clinical Oncology*, **23**, S48.

Pico J.L., Avila-Garavito A. & Naccache P. (1998) Mucositis: its occurrence, consequences, and treatment in the oncology setting. *The Oncologist* **3**, 446–451.

Pinto Marques A. & Branco A. (2011) Assessment of oral mucositis: comparative study. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Pomper L.J., Ostojic A., Jakovac R., Stuzic V., Zemljak S., Vukelic M., Zivotic I., Sikic I., Krpecanec M., Petkovic K., Farkas M., Vukorepa Z., Smiljanic M., Dubrovic N., Blazevic S., Elez T., Kvesic V. & Vrhovac R. (2011) Prophylaxis of oral mucositis in patients treated with haematopoietic stem cell transplantation. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Potting C., Van Groningen L., Theunissen K., Maertens J., Van Marwijk Kooy M., Schouten H., Visser O., Willems E., Sonnet A. & Blijlevens N. (2012) Caphosol in prevention of oral mucositis in autologous stem cell transplant recipients after high-dose melphalan (CASH). 38th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Quinn B., Stone R., Uhlenhopp M., McCann S. & Blijlevens N. (2007) Ensuring accurate oral mucositis assessment in the European Group for Blood and Marrow Transplantation Prospective Oral Mucositis Audit. *European Journal of Oncology Nursing* **11**, S10–S18.

Quinn B., Davies M., Horn J., Riley E., Treleaven J., Houghton D., Bealey A., McGowan C., Thomson M., Fulman L., Mais K., Feyer P., Hoy S. & Campbell F. (2012) *Mouth Care Guidance and Support in Cancer and Palliative Care. [Online]*. Available at: http://www.ukomic.co.uk

Rao N., Trotti A., Kim J., Schell M., Zhao X., Amdur R., Brizel D., Chambers M., Miyamoto C. & Rosenthal D. (2011) Phase II multicenter trial of Caphosol for the reduction of mucositis in patients receiving radiation therapy for head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* **81** (Suppl. 2), S75.

Recchia E., Chouchana L., Benitah C., Geneste E., Pippo N., Bompoint C., Adaeva R., Lapusan S., Rubio M.T., Joly A.C. & Rio B. (2011) High-dose chemotherapy and mucositis: nurses' and patients' points of view in an evaluation of supersaturated calcium phosphate oral rinse. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Rzepecki P., Waśko-Grabowska A., Oborska S. & Młot B. (2010) Use of a calcium phosphate mouth rinse for prevention of oral mucositis after haematopoietic stem cell transplantation: single-centre experience. 36th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Santos T., Marco M., Avellan E., Gutierrez M., Clemente M. & Hidalgo C. (2010) Advances in the control of oral mucositis during nurse visits. Spanish Oncology Nursing Society SEEO Congress.

Skorobogatova E., Dyshlevaia Z., Karachunsky A. & Pashanov E. (2011) First Russian experience of calcium phosphate mouth rinse usage for treatment of children with oral mucositis undergoing hematopoietic stem cell transplantation. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation.

Somé C., Hadri N., Federspiel I., Ngo Ton Sang B., Foroni L. & Calop J. (2009) Advantages of referencing Caphosol® for prophylaxis and treatment of chemotherapy-induced mucositis. Congress of the French Society of Oncology Pharmacy.

Sonis S.T. (2004a) Pathobiology of mucositis. *Seminars in Oncology Nursing* **20**, 11–15.

Sonis S.T. (2004b) Oral mucositis in cancer therapy. *The Journal of Supportive Oncology* **2**, 3–8.

Sonis S.T. (2009) Mucositis: the impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncology* **45**, 1015–1020.

Sonis S.T., Eilers J.P., Epstein J.B., Leveque F.G., Liggett W.H., Jr, Mulagha M.T., Peterson D.E., Rose A.H., Schubert M.M., Spijkervet F.K. & Wittes J.P. (1999) Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer* **85**, 2103–2113.

Stokman M., Burlage F. & Spijkervet F. (2010) The effect of a calcium phosphate mouth rinse on chemo/radiation induced oral mucositis in head and neck cancer patients. A prospective study. *Supportive Care in Cancer* **18**, S114; Abstract 08-075.

Stone R., Potting C.M.J., Clare S., Uhlenhopp M., Davies M., Mank A. & Quinn B. (2007) Management of oral mucositis at European transplantation centres. *European Journal of Oncology Nursing* **11** (Suppl. 1), S3–S9.

Thomson M. (2011) New study evaluating the effect of Caphosol in reducing oral mucositis in head and neck cancer patients undergoing chemo-radiotherapy or radiotherapy. [Online]. Available at: http://www.caphosol.ca/health-care-professionals/clinical-studies/Cached (accessed 30/11/2011).

Wardley A.M., Jayson G.C., Swindell R., Morgenstern G.R., Chang J., Bloor R., Fraser C.J. & Scarffe J.H. (2000) Prospective evaluation of oral mucositis in patients receiving myeloablative conditioning regimens and haemopoietic progenitor rescue. *British Journal of Haematology* **110**, 292–299.

Waśko-Grabowska A., Rzepecki P., Oborska S., Barzał J., Gawronski K., Młot B. & Szczylik C. (2011) Efficiency of supersaturated calcium phosphate mouth rinse treatment in patients receiving high-dose melphalan or BEAM prior to autologous blood stem cell transplantation: a single-center experience. *Transplantation Proceedings* **43**, 3111–3113.

Wolff A., Fox P.C., Ship J.A., Atkinson J.C., Macynski A.A. & Baum B.J. (1990) Oral mucosal status and major salivary gland function. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology* **70**, 49–54.

World Health Organization (1979) *Handbook for Reporting Results of Cancer Treatment*. Offset Publication, Geneva, Switzerland.

Yablonovich I., Donato M.L., Pecora A.L., Goldberg S.L., Feldman T., Goy A., Mato A.R. & Rowley S.D. (2010) Use of a supersaturated calcium phosphate mouth rinse for prevention and treatment of oral mucositis results in faster granulocyte recovery and hospital discharge than using a sodium bicarbonate rinse alone after autologous transplantation in the treatment of lymphoma. *Blood* **116**, Abstract 4517.

