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Caphosol® mouthwash gives no additional protection against oral mucositis compared to cryotherapy alone in stem cell transplantation. A pilot study

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A B S T R A C T

Purpose: To investigate if adding Caphosol®, a mouthwash solution, to oral cryotherapy (OC) further protects against oral mucositis (OM), a toxic painful complication to high dose chemotherapy.
Method: The study was a randomised, controlled, study design. Patients ≥16 years scheduled for allogeneic stem cell transplantation were included consecutively and randomised to experimental group receiving OC combined with Caphosol® ($n = 20$) or control group receiving OC only ($n = 20$). OC was given from start to end of HDCT. Caphosol®, from day 0 to day 21.
Result: There were no significant differences regarding age or gender between the groups. Mucositis was assessed with the World Health Organisation (WHO) grading scale. Pain was assessed with a 10 cm visual analogue scale (VAS) from 0 = no pain to 10 = worst imaginable pain. Start and duration of therapy with pain relieving drugs, serum C-reactive protein values, and number of days of hospitalisation were collected from the medical records. Data on OM, oral pain, use of i.v. opioids and total parenteral nutrition were collected during 22 days. There was no significant difference between the groups on OM, oral pain, use of i.v. opioids or TPN between the groups.
Conclusion: The study showed no additional effect of combining Caphosol® with OC.

Introduction

A common toxicity in haematopoietic stem cell transplantation (HSCT) is oral mucositis (OM). The POMA trial (Blijlevens et al. 2008) observed 44% of severe OM and an incidence level up to 87% of OM after Carmustine, Etoposide, Cytarabine and Melphalan (BEAM) and high-dose melphalan followed by autologous HSCT. In patients treated with myeloablative or high-dose melphalan combined with fludarabine as a reduced-intensity conditioning regimen in the setting of allogeneic HSCT therapy and allogeneic stem cell transplantation, OM is associated with more days of fever, increased risk of infection, higher use of total parenteral nutrition (TPN), more use of opioids and more days at hospital (Sonis et al. 2001; Svanberg et al. 2007, 2010; Aisa et al. 2005). Oral side effects, including OM, remain a source of illness despite the use of a variety of agents to treat them (Clarkson et al. 2010). Risk factors to develop oral mucositis have been classified into two categories, patient related and treatment related (Sonis, 2004; Cawley and Benson, 2005; Ellers and Million, 2007). There is a highly complex pathobiology behind mucositis. Inflammation leads to epithelial cell damage and death of the oropharyngeal mucosa resulting from chemotherapeutic agents and/or radiation. The damage on the submucosa is involved in a dynamic cascade of events. These events, elaborated by Sonis, can theoretically be divided into 5 stages: initiation, gene upregulation and message generation, amplification and signalling, ulceration and healing (Sonis 2004 (supplement)). An important pathway involved in the inflammatory response is the cyclooxygenase (COX) pathway and it can be directly activated by a number of chemotherapeutic drugs, including in the oral mucosa (Logan et al. 2007; Lalla et al. 2010). Antineoplastic agents also cause the release of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β and tumour necrosis factor (TNF) which can amplify further COX activation (Doi et al. 2002; Lin et al. 2006; Lalla et al. 2010). A number of interventions for preventing or treating mucositis have been proposed (Rubenstein et al. 2004). Oral cryotherapy (OC) (cooling the oral cavity) has been shown to reduce mucositis severity, the use of

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opioids and parenteral nutrition and to improve nutrition (Svanberg et al. 2007, 2010; Aisa et al. 2005). The effect has been ascribed to local vasoconstriction and reduction of blood flow to the oral mucosa, thereby hindering direct mucosal damage by cytotoxic chemotherapy (Lilleby et al. 2006; Svanberg et al. 2011). Caphosol® is a neutral supersaturated calcium phosphate (Ca^{2+}/PO_4^{-3}) mouthwash. It is proposed to exert a protective action against chemotherapy-induced mucositis the diffusion of ions into intracellular spaces in the epithelium and permeating mucosal lesions. When used in conjunction with topical fluoride treatments it has been shown in a prospective, double-blind, randomized trial, to significantly reduce mucositis associated with myeloablative therapy and radiation (Papas et al. 2003). However, to our knowledge, a combination of oral cryotherapy and Caphosol® has not yet been studied. Since the mechanism of action is different for cryotherapy and Caphosol®, our hypothesis was that the combined prophylaxis might have an added beneficial effect to reduce oral mucositis as compared to cryotherapy alone. The aim of the present study therefore was to investigate if Caphosol® mouth rinsing as a complement to standard oral care including OC, would further reduce oral mucositis in connection with conditioning chemotherapy for stem cell transplantation.

Material and methods

Design

The study was a randomised, controlled, open-label study design where patients were randomised either to standard treatment including OC or standard treatment including OC and Caphosol®. OC was given in the form of ice cubes or crushed ice to be kept in the mouth during the actual infusion of the HDCT. Thirty (30) ml Caphosol® was administrated for rinsing the whole oral cavity four times/day starting prior to HDCT and ending day 21. The randomization was made by a random computer table by an independent nurse.

Subjects

Qualified to participate in the study were patients >16 years of age, able to communicate in Swedish, scheduled for allogeneic stem cell transplantation (SCT) at the Akademiska University Hospital in Uppsala, Sweden. Fifty-two consecutive patients were invited to participate in the study between September 2010 and October 2011. Eight patients wanted only standard oral care and declined to participate, four of them due to fear of nausea. The final sample consisted of 40 patients, 20 randomised to the control (CTR) group and 20 to the experimental (EXP) group. No significant difference was found regarding gender or age between the CTR and EXP groups. There were seven different diagnoses evenly distributed between EXP and CTR (Table 1).

Medical treatment

All patients received intravenous conditioning chemotherapy and (when required) total body irradiation (TBI) on the basis of diagnosis. Supportive care and conditioning therapy was performed according to hospital practice. Ten patients (EXP $n = 5$, CTR $n = 5$) received reduced-intensity conditioning for transplantation (RICT) regimes. There were no significant differences between EXP and CTR group regarding conditioning therapy (Table 1). Conditioning therapy regimes are presented in the Appendix. The i.v. pain relief used was morphine (opioid). Other, orally administrated, pain medications were, for example, tablet morphine (opioid), tramadol (weak opioid), tablet/mixtures/i.v. Paracetamol (peripherally acting analgesic) or viscose/mouth rinse for local oral pain relief.

Table 1
Patient characteristics and diagnoses.

	Experimental group $n = 20$	Control group $n = 20$	Total
Female/Male	9/11	8/12	40
Age, mean ± SD	50.4 ± 10.6	49.6 ± 13.2	
Diagnosis			
AML	7	8	15
ALL	4	2	6
CLL	1	4	5
CML, CMML	2	1	3
MDS	2	3	5
Myeloma, Myelofibrosis	2	0	2
Lymphoma	2	2	4

AML = Acute myeloid leukaemia, ALL = Acute lymphoblastic leukaemia, CLL = Chronic lymphatic leukaemia, CML = Chronic myeloid leukaemia, CMML = Chronic myelomonocytic leukaemia, MDS = Myelodysplastic syndrome.

Procedure

Patients scheduled for SCT at the Akademiska University Hospital in Uppsala, Sweden, were offered to participate in the study. The nurse responsible for the study presented the information orally and in writing when the patients arrived to the ward. Patients who agreed to participate gave their written consent and were randomly assigned to the EXP or the CTR group. Mucositis was assessed with the World Health Organisation (WHO) mucositis grading scale combining objective signs of mucositis (erythema and ulcer formation) with subjective and functional outcomes (pain and ability to eat) (World Health Organization, 1979). A nurse in charge of the study patient examined the oral cavity daily as part of the morning routine care from the start of chemotherapy until day 21. Pain was assessed with a 10 cm visual analogue scale (VAS) from 0 = no pain to 10 = worst imaginable verbally twice a day and recorded by the nurse in charge. Information about the start and duration of therapy with i.v. opioids and other pain relieving drugs, serum C-reactive protein (CRP) values, and number of days of hospitalisation were collected from the medical records.

Nutritional status was measured as weight, body mass index (BMI), S-albumin (reference values 36–48 g/l) and start and number of days with TPN. Renal function was measured as S-creatinine (reference value, men 60–105 μmol/l, women 45–90 μmol/l).

The study was approved by the regional Research Ethics Committee, D.no; 2010/134.

Data analysis

The analysis was made on an intention-to-treat basis. EXP and CTR groups were compared in the total material. Outcomes between the two groups were compared using an analysis of serial measurements utilising the area under the curve (AUC). This summary measure is calculated by adding the areas under the graph (where outcome score is plotted against time) between each pair of consecutive observations, for each outcome measure, for each subject. The AUC values of the groups were then compared using Mann–Whitney *U* tests. For comparison between EXP and CTR groups, the unpaired *t*-test and the Mann–Whitney *U*-test was applied. A P value <0.05 was considered statistically significant.

Results

There were no severe oral symptoms among patients ($n = 40$) included in the study at day 0 that could be attributed to OM. Oral