

A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation

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Summary:

Oral mucositis is a complication common to many cancer therapies and produces considerable pain and morbidity. The present study reports a double-blind, prospective, randomized clinical trial testing the efficacy of a calcium phosphate mouth rinse (Caphosol[®]) with fluoride treatments vs a standard regimen of fluoride rinsing and placebo tray treatments in 95 patients undergoing hematopoietic stem cell transplantation (HSCT). The days and severity of mucositis were prospectively evaluated. There were statistically significant decreases in days of mucositis (3.72 vs 7.20 $P=0.001$), duration of pain (2.86 vs 7.67, $P=0.0001$), dose of morphine (30.46 mg vs 127.96 mg), days of morphine (1.26 vs 4.02, $P=0.0001$) and days to the onset of engraftment ANC (absolute neutrophil count) $>200\text{ mm}^3$ (11.12 vs 12.56) in the Caphosol[®] and fluoride treatment group vs fluoride-rinse group, respectively. Caphosol[®], a neutral, super-saturated, $\text{Ca}^{2+}/\text{PO}_4^{3-}$ mouth rinse, used in combination with topical fluoride treatments, is superior to fluoride rinse alone in reducing the frequency, intensity and duration of oral mucositis in patients undergoing HSCT. *Bone Marrow Transplantation* (2002) 00, 000–000. doi:10.1038/sj.bmt.1703870

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High-dose chemotherapy administered as part of the preparative regimens prior to hematopoietic stem cell transplantation (HSCT) has a direct cytotoxic effect on the oral epithelium leading to injury or disruption of the mucosal barrier. Factors involved in the disruption of the oral barrier include the type of agents used in the preparative regimen, elaboration of cytokines and use of oral preventive measures as well as the individual patient's response.^{1,2} Mucositis is associated with an increase in the incidence of systemic infections because of disruption of the natural mucosal barrier and impacts both length of hospital

stay and the complications associated with HSCT.^{3,4} Sonis *et al*⁴ in a multicenter study, using the Oral Mucositis Assessment Scale (OMAS), reported that mucositis was correlated with risk for infection, mortality, days of injectable narcotics, and hospital stay and charges. The total cost for hospitalization was \$43 000 more for patients with ulceration.

HSCT is frequently associated with saliva hypofunction. Saliva provides a tissue-coating film, which is responsible for antimicrobial protection. Saliva lubricates the mucosa and helps maintain the integrity of the oral cavity through its mineralizing potential. Oral mucositis and infections from oral microorganisms are a major cause of morbidity and mortality following bone marrow transplantation.² Mucositis is one of the major causes of severe pain and debilitating toxicity associated with high-dose chemotherapy and radiation therapy, and occurs in the majority of autologous and allogeneic HSCT recipients, despite current oral hygiene regimens.^{2,4–6}

Sources of infection include pre-existing periodontal disease, pericoronitis or periapical abscess, which may progress following high-dose chemotherapy.^{4,7,8} Current oral health practices place a heavy emphasis on the prevention of oral disease, a process that should begin well in advance of chemotherapy and/or radiation therapy in an attempt to reduce intraoral bacterial counts and prevent superinfection of mucosal ulcers.

The preferred regimen for the prevention of oral mucositis for patients receiving an HSCT remains unclear. A number of studies have attempted to evaluate different agents or strategies to prevent or treat mucositis associated with high-dose chemotherapy, with conflicting results (Table 1).^{9–27} Prior studies on oral health-care management in oncology patients undergoing head and neck radiation, with or without chemotherapy, have suggested that a preventive regimen designed to address the reduced salivary flow and/or xerostomia was effective in reducing and controlling both the incidence and severity of mucositis.^{9,28} The system used in these prior studies consisted of a high fluoride gel administered together with a neutral super-saturated $\text{Ca}^{2+}/\text{PO}_4^{3-}$ mouth rinse (Caphosol[®]).^{29,30} In two single-arm studies evaluating patients receiving HSCTs and head and neck radiation therapy, the Caphosol[®]-based oral health management system was well tolerated and was associated with an improvement in oral mucositis as compared with previous controlled studies.^{31,32} These

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Table 1 List of past and current strategies

Treatment	Agent	Results
Topical	NaHC ₀₃ /Nacl Standard hospital regimen	Negative
		Papas and Johansen ⁹ Ezzone <i>et al</i> ¹⁰
	Chlorhexidine	Mixed results
		Ferretti <i>et al</i> (+) ¹¹
		Samaranayake <i>et al</i> 1988 (-) ¹²
		Foote 1994 (-) ¹³
	Hydrogen peroxide	Negative
		De Walt and Haines, 1969 ¹⁴
	IB-367 = a naturally occurring antimicrobial agent derived from porcine neutrophil peptides	Positive
		Vesole and Fuchs ¹⁵
Systemic	Glutamine	Mixed results
		Anderson <i>et al</i> (-) ¹⁶ Schloerb and Skikne (+) ¹⁷
	Interleukin-11	Positive
		Sonis <i>et al</i> ¹⁸ Schwerkoske <i>et al</i> ¹⁹
	KGF = keratinocyte growth factor	Positive
		Durrant <i>et al</i> ²⁰
	GM-CSF = granulocyte macrophage colony- stimulating factor	Mixed results
		Atkinson <i>et al</i> ²¹ (no difference)
	G-CSF = granulocyte colony- stimulating factor	Nemunaitis <i>et al</i> (+) ²²
		Positive
Amifostine	Gabrilove <i>et al</i> ²³ Crawford <i>et al</i> ²⁴	
	Mixed results	
	List (+) ²⁵ Capelli <i>et al</i> (+) ²⁶ Chauncey <i>et al</i> ²⁷ (negative for mucositis)	

favorable results suggested the need for a controlled, prospective clinical trial. This report presents the results of a prospective, double-blind, randomized trial comparing a Caphosol[®]-based regimen to a commonly used standard regimen of fluoride rinses alone in patients undergoing autologous or allogeneic HCST.

Methods

A total of 97 patients who were to receive an HSCT were enrolled in the study. Two patients (one from each arm) did not comply with the protocol and were removed from the study. The study dentist and periodontist evaluated all patients prior to their scheduled transplant. All patients gave informed consent approved by The Institutional Review Board (IRB). The study was double-blinded and patients were randomized and stratified by the type of transplant: autologous or allogeneic (Tables 2 and 3). Table 3b shows the conditioning regimens of the two treatment groups. As can be seen the two groups had similar regimens. All autologous transplant patients received peripheral stem cells and granulocyte colony stimulating factor (G-CSF). All allogeneic patients received bone marrow transplants and the identical short course of methatrexate (12 mg/m² on day one and 10 mg/m² on day three) to prevent graft-*versus*-host disease (GVHD). All

Table 2 Disease category and treatment group assignment

	Caphosol/F Mean age 43 (19-69)	Fluoride rinse Mean age 42 (18-70)
Total number of patients (95)	50 (24 males/ 26 females)	45 (25 males/ 20 females)
Acute lymphocytic leukemia	4	2
Acute myelogenous leukemia	8	8
Chronic myelogenous leukemia	6	5
Hodgkin's disease	7	3
Non-Hodgkin's lymphoma	8	12
Multiple myeloma	8	6
Myelo dysplastic syndrome	4	2
Breast cancer	3	4
Ovarian cancer	1	0
Other	1	3

Table 3

(a) Transplant category

	Autologous	Allogeneic
Total # of patients	50	45
TBI (total body radiation)	9	41
Group I	27	23
Group I, TBI	6	21
Group II	23	22
Group II, TBI	3	20

(b) Conditioning regimens

	Caphosol/F	Fluoride rinse
Total Number of patients (95)	50 (24 males/ 26 females)	45 (25 males/ 20 females)
TBI	27	23
Melphalan	18	16
Cytosan	3	3
VP16-BUC	2	2
EPA/Carboplatinum	0	1

total body radiation (TBI) patients received 1200 cGy given over the 3 days before transplantation on a BID regimen. Both treatment groups received identical oral hygiene instructions for brushing, flossing and rinsing. A thorough oral examination was performed. A complete baseline evaluation, directed at detecting and eliminating existing and potential sources of infection, such as caries and periodontal disease, was performed on all patients. The patient's home-care practice was evaluated and improved as deemed necessary. Both whole unstimulated and paraffin-stimulated saliva samples were taken to assess salivary flow rate. Patients were told not to eat or drink for one and one-half hours prior to the morning visit. All potential sources of trauma were removed, such as orthodontic braces and ill-fitting prostheses. All patients received the standard prophylactic transplant regimen, which includes acyclovir prophylaxis for herpes simplex virus in seropositive patients, and the protocol-designated antifungal prophylaxis.

All patients were asked not to brush their teeth overnight and were given a screening microbiology test for *S. mutans* and *Lactobacillus*. *S. mutans* (Caphosol[®]) 177242 ± 5888808 *vs* fluoride 2488911 ± 1359390, *P* = 0.2066) and

Lactobacillus counts (Caphosol[®]) 2590235 ± 1794144 vs fluoride 209742 ± 97848 , $P = 0.7589$) were not significantly different for the two groups. Additionally, all patients had dental prophylaxis advice at the screening visit and those who had high counts were treated with chlorhexidine prior to hospitalization. The study participants were assigned their study rinse by the pharmacist on admission to the transplant unit. The rinses were administered four times a day by the trained, unit nurses. The study patients were followed until engraftment and the resolution of mucositis, by a single dentist trained for this study. A backup calibrated dental examiner also went through the training process.

The patients were randomized to either Group 1 or 2.

Group 1: Caphosol[®]-neutral $\text{Ca}^{2+}/\text{PO}_4^{3-}$ rinse. Prior to HSCT, this group received four topical fluoride treatments of 1% F as neutral 2% NaF gel administered by tray at the screening visit and completed prior to hospitalization. During the transplant, patients used a $\text{Ca}^{2+}/\text{PO}_4^{3-}$ rinse (Caphosol[®]) at least four times daily, 30 ml each time. The composition of the Caphosol[®] rinse is: Ca^{2+} , 4.74 mM, PO_4^{3-} , 2.96 mM, Na^+ , 97.67 mM, Cl^- , 116.6 mM, and pH 7.1.

Group 2: Control arm – aqueous NaF 0.01% rinse. Prior to transplant, this group received four topical treatments with a placebo gel that was administered by the same technique as in group 1. During the transplant, the patients used the aqueous NaF 0.01% rinse at least four times daily, 30 ml each time.

Patients in either group who developed severe mucositis were instructed to rinse up to 10 times a day with their respective solutions. The rinses were packaged in identical containers. The study dentist, nurses and the pharmacist monitored compliance.

During the trial, the study dentist examined all hospitalized patients three times per week. Mucositis was judged using the following scale devised by the National Institute of Dental and Craniofacial Research (NIDCR):^{33,34}

Score:	Clinical finding
0	No change
1	Erythema
2	Single ulcer < 1 cm
3	A few ulcers approximately 1 cm
4	Multiple ulcers > 1 cm
5	Slough

This scale was used to determine the days of mucositis (Score > 1), as well as peak mucositis (highest individual score). The scale has been used at the study location since 1985. This study was started in 1998 before the OMAS scale was validated and published by Sonis *et al* in 1999.³⁵

Data on engraftment were obtained from the daily, complete blood count reports entered in the patient's medical record. An absolute neutrophil count (ANC) of 200 cells/mm^3 was considered the time point for neutrophil engraftment in this study.

Pain was assessed by patients using a 0–100 Visual Analog Scale (VAS) where 100 = most pain imaginable. Patients subjectively rated their pain in a daily log with nurses or the study dentist assisting them. Patients were asked to differentiate oral pain from that of other origins

(eg, esophageal). The days of pain (scores > 0) and peak pain-highest score were obtained from these logs.

Systemic analgesia administered for control of oral pain resulting from mucositis was intravenous morphine sulfate (MSO_4). Both the total amounts in milligrams and the number of days the patient required intravenous morphine were recorded.

The study entry days post-transplant represents the days of hospital stay following the infusion of the hematopoietic stem cells (day 0 = day of the transplant).

Days of fever were recorded as a surrogate marker for infection.

Statistical methods

In total, 147 patients were screened and among them 97 were enrolled. Two patients, one from each arm were disqualified. One refused to use the rinses and the other was too ill to participate. Both groups were equally compliant with using the rinses. One person per group was partially compliant. We attribute the high level of compliance to the diligence of the nursing staff on the Bone Marrow Transplantation Unit of NEMC and the importance they ascribed to oral health.

The data from 95 available patients, evaluating nine selected study variables were analyzed according to the procedures of 2×2 factorial ANOVA or nonparametric Mann–Whitney U-tests, appropriate to data distributions and/or the scale of measurement (interval or rank order) of the variables. All results represent the analysis by intent to treat.

Power efficiency was estimated on data from the first year of the study. It was determined that approximately 50 patients per treatment group (balanced for type of transplantation) would be needed to achieve α and β rates of at least $P = 0.05$ – power of 95% for all principal variables but the number of days to reach $\text{ANC} > 500 \text{ mm}^3$, which would have taken about 350 patients per treatment group and was beyond the fiscal and staffing constraints of this study. The differential of sample size is, of course, because of extreme individual differences in achieving engraftment. Power calculations were repeated after the second year of study and found to be stable and conservative.

Results

Results for the 11 principal variables are described separately in the summary Tables 4a and b and Figures 1–4. Tables 4a and b give both descriptive statistics and treatment comparisons for the 11 study variables. Figures 1–4 graphically describe the treatment effects over time.

Days to $\text{ANC} > 200 \text{ mm}^3$. (onset of neutrophil engraftment): ANOVA for factorial designs was chosen for the analyses of $\text{ANC} > 200 \text{ mm}^3$. Factors were treatment (Caphosol[®] vs Fluoride rinse) and type of transplant (autologous or allogeneic). Table 4a and Figure 1 show the mean number of days to reach $\text{ANC} > 200 \text{ mm}^3$. The days to an $\text{ANC} 200 \text{ mm}^3$ were significantly different for the two treatment Groups (11.12 vs 12.56 days, for Groups 1 and 2,

Table 4 Comparisons of treatment (a) and bone marrow factor (b) (Subgroups of autologous/allogeneic combined)

Variable	(A) Caphosol rinse		Fluoride rinse		Test statistic	P
	Mean \pm s.e.	Median range	Mean \pm s.e.	Median range		
Days to ANC <200	11.12 \pm 0.41	10.0 (6.00–18.00)	12.56 \pm 0.61	12.00 (7.00–28.00)	ANOVA F = 5.88	<0.00173
Days to ANC <500	13.26 \pm 0.59	12.00 (8.00–25.00)	14.58 \pm 0.91	13.00 (7.00–38.00)	ANOVA F = 1.68	<0.1983
Days of mucositis	3.72 \pm 0.58	3.0 (0.00–15.00)	7.22 \pm 0.86	7.00 (0.0–20.00)	ANOVA F = 11.65	<0.00096
Days of ulceration	2.18 \pm 0.49	0.0 (0.0–13.00)	5.27 \pm 0.86	4.5 (0.0–20.00)	ANOVA F = 10.29	<0.0019
Peak level of mucositis	1.38 \pm 0.21	1.0 (0–5)	2.41 \pm 0.261	3.00 (0.00–5.00)	Mann–Whitney U = 726 ^a	<0.004
Peak level of pain	19.80 \pm 4.28	0.0 (0.00–100.00)	50.33 \pm 5.16	60.0 (0.00–100.00)	Mann–Whitney U = 546 ^a	<0.0001
Days of pain	2.86 \pm 0.61	0.0 (0.0–15.00)	7.67 \pm 0.82	7.0 (0.0–21.00)	ANOVA F = 22.11	<0.0001
Total morphine (MG) for mucositis	34.54 \pm 11.94	0.0 (1–400)	122.78 \pm 24.57	88.00 (0.0–812)	Mann–Whitney U = 606.5	<0.0001
Days of morphine	1.26 \pm 0.36	0.0 (0.0–11.00)	4.02 \pm 0.70	3.0 (0.0–22.00)	Mann–Whitney U = 662.5 ^a	<0.00015
Days post-BMT	24.48 \pm 2.47	17.0 (10–71)	24.79 \pm 2.45	18.0 (11–79)	ANOVA F = 0.00	<0.9447
	(B) Autologous		Allogeneic			
	Mean \pm s.e.	Median range	Mean \pm s.e.	Median range		
Days to ANC <200	9.68 \pm 0.27	9.50 (6.00–18.00)	14.16 \pm 0.52	14.00 (7.00–28.00)	ANOVA F = 65.09	<0.0001
Days to ANC <500	11.14 \pm 0.62	10.00 (7.00–38.00)	16.93 \pm 0.91	16.00 (10.00–28.00)	ANOVA F = 41.65	<0.0001
Days of mucositis	5.06 \pm 0.69	4.00 (0.00–17.00)	5.73 \pm 0.85	5.00 (0.00–20.00)	ANOVA F = 0.34	0.5587
Days of ulceration	3.45 \pm 0.64	2.00 (0.00–13.00)	3.82 \pm 0.79	0.00 (0.00–20.00)	ANOVA F = 1.05	0.3084
Peak level of mucositis	1.98 \pm 0.24	2.00 (0.00–5.00)	1.73 \pm 0.26	1.00 (0.00–5.00)	Mann–Whitney U = 999.5 ^a	0.4273
Peak level of pain	35.50 \pm 4.96	35.00 (0.00–100.00)	32.89 \pm 5.46	20.0 (0.00–100.00)	Mann–Whitney U = 1079.5 ^a	0.7296
Days of pain	5.09 \pm 0.83	2.00 (0.00–21.00)	5.18 \pm 0.77	5.00 (0.00–17.00)	ANOVA F = 0.05	0.8290
Total morphine (MG)	73.18 \pm 18.86	0.00 (0.00–812.00)	78.87 \pm 19.28	0.00 (0.00–488.00)	Mann–Whitney U = 1077 ^a	0.8516
Days of morphine	2.40 \pm 0.49	0.00 (0.00–13.00)	2.76 \pm 0.66	0.00 (0.00–22.00)	Mann–Whitney U = 1113.5 ^a	0.9281
Days post-BMT	15.64 \pm 0.81	15.00 (10.00–32.00)	35.83 \pm 3.14	30.50 (16.00–79.00)	ANOVA F = 39.34	<0.0001

^aNonparametric test used because of non-normality of data.

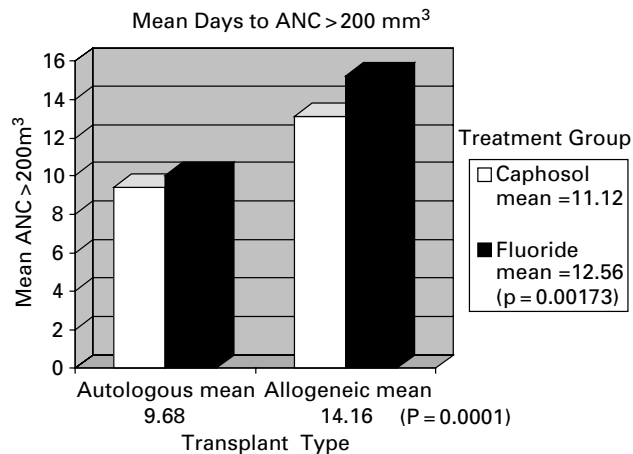


Figure 1 (Days to ANC > 200 mm³) The Caphosol[®] group had a statistically significant lower mean number of days (11.12 days) to ANC > 200 compared to fluoride rinse (12.56 days); $P < 0.00173$. Mean number of days to ANC > 200 were statistically significantly less for autologous patients (9.68 days) vs allogeneic patients (14.16 days) in both treatment groups; $P < 0.0001$.

respectively; $P = 0.00173$). Autologous patients achieved ANC > 200 mm³ 4 days earlier than the allogeneic patients, but patients undergoing both transplants appeared to benefit from treatment with Caphosol[®].

Days to ANC > 500 mm³ (engraftment). The ANOVA for factorial designs was again appropriate for statistical analyses of this variable. Table 4a and b give the descriptive and comparative statistics for ANC > 500 mm³. No significant difference was found between treatment groups (13.26 vs 14.58 days for Caphosol[®]) vs F rinse, respectively;

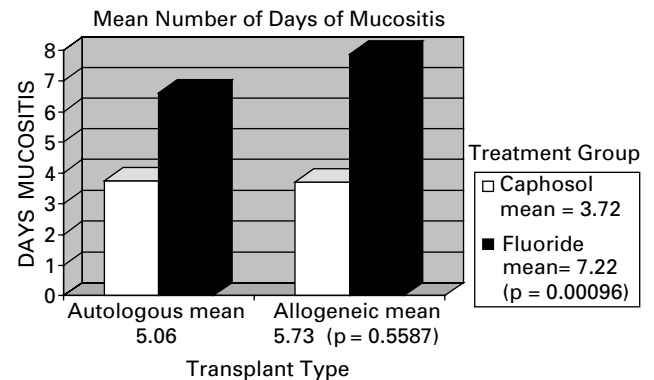


Figure 2 (Days of mucositis) The Caphosol[®] group had a statistically significant lower mean number of days (3.72) of mucositis compared to fluoride-rinse group (7.22); $P < 0.00096$. Mean number of days of mucositis was not significantly different for the autologous (5.06) vs allogeneic (5.73) transplant groups; $P = 0.5587$.

$P = 0.1983$). Autologous patients reached engraftment 5.8 days earlier than allogeneic patients ($P < 0.0001$). Mean differences between treatments remained in favor of Caphosol[®].

Days of mucositis. Duration of mucositis for all patients was 3.5 days longer for patients in the fluoride-rinse control arm (7.20 days) vs the Caphosol[®] group (3.72 days); $P = 0.00096$ (Table 4a, Figure 2). Type of transplant, allogeneic vs autologous, had no significant effect on the difference between the treatments. A total of 40 vs 19% of patients had no mucositis in the Caphosol[®] and the control arms, respectively.

Days of mucositis for both the allogeneic and autologous patients were comparable in the Caphosol[®] arm but longer

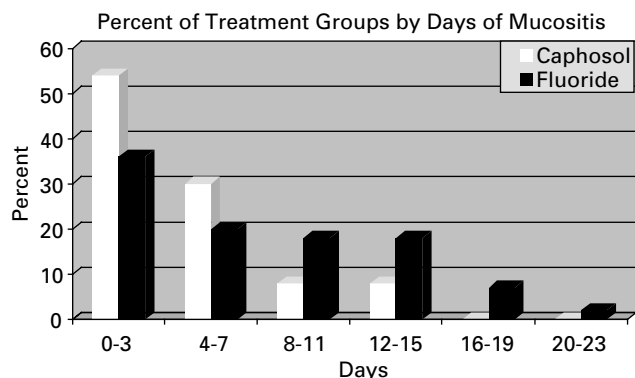


Figure 3 (Percentage of treatment groups by days of mucositis) A higher percentage of Caphosol[®] users had fewer days of mucositis compared to the fluoride-rinse group.

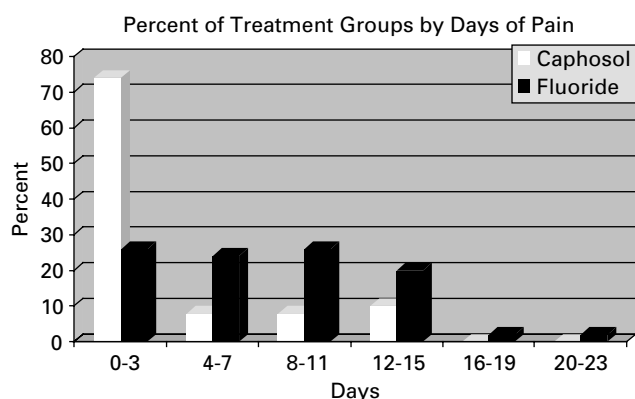


Figure 4 Percentage of treatment groups affected by days of pain) A higher percentage of Caphosol[®] users had fewer days of pain compared to the fluoride-rinse group.

for patients undergoing an allogeneic transplant than those in the autologous control arm. Also, there was a shift in the overall distribution to fewer days of greater than grade 1 mucositis for all the patients receiving Caphosol[®] (Figure 3). Days of ulceration were also analyzed separately for mucositis with similar findings (Table 4a).

Peak mucositis. Peak mucositis was determined by the NIDCR scale. Nonparametric statistics, using the Mann–Whitney U-test corrected for samples over 20, was used. All possible combinations of subgroups of treatments and HSCT type were compared (Table 4). The maximum (peak) level of mucositis was significantly higher for patients in the control group (MDN = 3.0) than for the Caphosol[®] group (MDN = 1.0); $P = 0.004$.

Peak pain. Peak pain was a variable in a rank score based upon patient judgment. Nonparametric Mann–Whitney U-tests were used to evaluate all combinations of factors. The mean peak level of pain was 19.8 and 50.33 for the Caphosol[®] and fluoride-rinse groups, respectively ($P < 0.0001$). There was a shift to fewer days of pain for all patients on Caphosol[®] (Figure 4).

Days of pain. A significant reduction in days of pain experienced by patients was observed in the Caphosol[®]

treated patients (2.86) vs fluoride-rinse patients (7.67 days); $P < 0.001$ (Table 4a).

Milligrams of self-administered morphine. There was a significant ($P = 0.0001$) reduction in total milligrams of morphine used during mucositis by patients in the Caphosol[®] group (mean = 34.54 mg) vs fluoride rinse alone (mean = 122.78 mg). Parametric analysis was complimented by nonparametric Mann–Whitney procedures because of the extreme skew in data distributions (Table 4a). Median values are preferred measures of central tendency in such cases. The strong skew was produced by the large percentage of patients who required no morphine in the Caphosol[®] group (74 vs 34.1 % for the fluoride-rinse group). Caphosol[®] MDN = 0 vs fluoride-rinse MDN = 88.00 mg ($P < 0.00015$).

Days of morphine. There was a significant difference in days of morphine use in the patients receiving Caphosol[®] (mean = 1.26) vs fluoride-rinse patients (mean = 4.02 days); $P = 0.0003$. Median days of morphine use by Caphosol[®] patients (median = 0) was significantly less than the fluoride-rinse patients (median = 3.00); $P = 0.00015$ by Mann–Whitney U-test (Table 4a).

Days post-BMT. The hospital stay post-stem-cell infusion was significantly longer overall for the allogeneic patients than for the autologous patients (35.833 vs 15.639 days, respectively; $P < 0.0001$). However, there was no significant difference with regard to the length of hospital stay between the Caphosol[®] and the fluoride-rinse group; $P = 0.9447$ (Table 4b).

The days of fever were analyzed as a surrogate variable for infection and were found not to be significantly different for each group (Caphosol[®] 3.18 ± 0.54 and fluoride 2.73 ± 0.55 $P = 0.566$). One death occurred in the fluoride group during the study because of an aspergillus infection.

Discussion

The findings in this study confirmed our previous observation that the calcium phosphate regimen (Caphosol[®]) administered with topical fluoride treatments has a significant effect on ameliorating the oral mucositis, which is associated with radiation and/or chemotherapy.^{9,28–32} In the patients undergoing an HSCT, it was observed that the frequency, duration and severity of the oral inflammatory process was significantly less in the Caphosol[®] group than in the control group. The other beneficial effects such as reduced pain and a decreased use of morphine were also observed. These effects were expected as consequences of the reduced intensity of the mucositis.

Although we observed a decrease in the number of days to ANC > 200 mm³ in the Caphosol[®] group, there are no data to suggest that Caphosol[®] directly affected the total white blood count, and ANC > 500 mm³ was not significantly different in the Caphosol[®] group as compared to the fluoride-rinse group. The decreased time to ANC > 200 mm³ may be a manifestation of the decreased

mucositis resulting in less margination of neutrophils to the site inflammation. An ANC of 200 mm³ was chosen as the earliest point for neutrophil engraftment because it was thought that the effect of an agent to ameliorate the effects of mucositis would be most prominent prior to full neutrophil engraftment (ANC > 500 mm³).

The randomized, double-blind, experimental design of this study of patients at risk for mucositis required the inclusion of a control arm with established benefits to oral health. A commercially available aqueous rinse containing 0.01% NaF was chosen. It is known that such an NaF solution will cause fluoride deposition on calcified dental tissues and therefore impart an increased resistance to dental caries. Tooth surfaces treated topically with a fluoride preparation also show a reduced degree of bacterial plaque deposition under normal circumstances. By this means, foci of bacterial colonization are reduced. Furthermore, the fluorine ion inhibits certain enzymatic processes in microorganisms, making it bacteriostatic or bacteriocidal depending upon the fluoride ion concentration.³⁶ At the fluoride level of 100 ppm as used here, such an effect should come into play, possibly benefiting patients by reducing the chance of infection, although it is known that microorganisms can adapt to high concentrations of fluoride.³⁷ In another recent study using the antimicrobial agent IB-367, favorable results were noted in terms of reduced incidence of mucositis.¹⁵ However, considering that the topical use of such proven antibacterial agents as chlorhexidine and hydrogen peroxide gave predominately negative results, this points to the limited value of the antimicrobial approach alone.¹²⁻¹⁴ Moreover, the use of these agents may adversely affect the mucosa while curtailing microbial growth. With regard to the cytoprotective activity of amifostine, it has been shown to reduce mucositis and complications associated with high-dose chemotherapy in some studies.²⁵⁻²⁷ However, unlike amifostine, which is systemically administered, the agents used in this trial were all topical and therefore not associated with systemic side effects.

Unlike other regimens, the system of mucositis management evaluated in the Caphosol[®] group used a dual phase approach. The pre-transplant treatment with a 1% fluoride gel (2.24% NaF), followed by repeated Caphosol[®] rinses permitted the deposition of substantial amounts of fluoride in the dental tissues. This accepted procedure also caused remineralization of active carious lesions and resulted in a cleaner tooth surface with fewer areas of bacterial growth (plaque deposits), possibly decreasing the chances of infection.^{29,30} As in the Sonis *et al*⁴ study, the fact that fever and infection were not significantly different in the two study groups may be explained by greater frequency and severity of other transplant-related complications obscuring the impact of mucositis.

During the patient recovery period Caphosol[®] was the sole agent used. The distinguishing feature of Caphosol[®] compared to the other rinses and agents tested (Table 1) is its high concentration of Ca²⁺ and PO₄³⁻ ions. It is hypothesized that these ions, because of their high concentration, exert their beneficial effects by diffusing into intercellular spaces in the epithelium and permeate the mucosal lesion in mucositis. The Ca²⁺ ion plays a crucial

role in several aspects of the inflammatory process, the blood clotting cascade and tissue repair. Changes in intracellular Ca²⁺ by release of cytosolic Ca²⁺ and influx of extra cellular Ca²⁺ effect leukocyte chemotaxis, modulation of adhesion molecules and elaboration of arachidonic metabolites including prostaglandins, leucotrienes and lipoxins.³⁸⁻⁴¹ These latter agents influence the inflammatory process and leukocyte adhesion. Prostaglandins are also involved in the pathogenesis of pain and fever in inflammation.⁴² Furthermore, the Ca²⁺ ion together with the protein calmodulin plays a role in nitric oxide production in endothelial cells, which affects vasodilatation, inhibits platelet aggregation and regulates leukocyte influx.⁴³ The Ca²⁺ ion is also central in several of the enzymatic steps leading to the production of fibrin.⁴⁴ It further has an important function in tissue repair and regulation by being an essential part of the intracellular signal transduction system that brings about cell growth and metabolism.⁴⁵

The availability of inorganic phosphate is also essential for the biochemical processes related to mucositis. It is a key building block of the organic phosphates ubiquitously present both extracellularly and intracellularly, the source being the ionized phosphate component of the plasma buffering system. In the present study, Caphosol[®] as used in the management of oral mucositis might be a valuable supplemental source of phosphates for damaged mucosal surfaces.

The authors acknowledge that this study was conducted at a single center on a limited number of patients receiving multiple, different regimens. However, the regimens used and patients treated are similar to other studies of patients receiving HCSTs. The results of this double-blind, randomized prospective study are similar to those reported in prior retrospective studies evaluating Caphosol[®].

Conclusion

In conclusion, the oral solution of neutral supersaturated Ca²⁺/PO₄³⁻ (Caphosol[®]) used in conjunction with four fluoride tray treatments was found to be a significant adjunct in the management of mucositis associated with high-dose chemotherapy and radiation therapy. In this prospective, double-blind, randomized trial, a Caphosol[®] treatment program was associated with a significant decrease in the number days of mucositis, peak level of mucositis and days requiring morphine. Caphosol[®] in conjunction with fluoride trays was superior to fluoride rinses alone in reducing the frequency, intensity and duration of oral mucositis and ameliorating the morbidity associated with HSCT, decreasing the time to the onset of engraftment. The use of Caphosol[®] should be considered in the treatment of patients undergoing HSCT at high risk of mucositis.

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