Double-Blind, Placebo-Controlled, Randomized Study of Chlorhexidine Prophylaxis for 5-Fluorouracil-based Chemotherapy-induced Oral Mucositis With Nonblinded Randomized Comparison to Oral Cooling (Cryotherapy) in Gastrointestinal Malignancies

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BACKGROUND. The purpose was to evaluate prevention of oral mucositis (OM) using chlorhexidine compared with placebo and with oral cooling (cryotherapy) during fluorouracil (5-FU)-based chemotherapy in gastrointestinal (GI) cancer.

METHODS. Patients with previously untreated GI cancer receiving bolus 5-FU/leucovorin chemotherapy were randomized to chlorhexidine mouthrinse 3 times a day for 3 weeks (Arm A), double-blind placebo (normal saline) with the same dose and frequency (Arm B), or cryotherapy with crushed ice 45 minutes during chemotherapy (Arm C). Patients self-reported on severity (CTC-grading) and duration of OM.

RESULTS. Among 225 patients randomized, 206 answered the questionnaire (70, 64, and 63 patients in Arms A, B, and C, respectively) and were well balanced with respect to diagnoses, stage, age, sex, smoking habits, and performance status. Mucositis grade 3–4 occurred more frequently in Arm B (33%) than in A (13%, $P < .01$) and C (11%, $P < .005$). Duration was significantly longer in B than in both A ($P = .035$) and C ($P = .003$).

CONCLUSIONS. The frequency and duration of OM are significantly improved by prophylactic chlorhexidine and by cryotherapy. The latter is easy and inexpensive but has limited use, as it is drug- and schedule-dependent. The current study is the first double-blind randomized evaluation of prophylactic chlorhexidine in a large adult patient population with solid tumors receiving highly OM-inducing chemotherapy. A role for chlorhexidine in the prevention of OM is suggested, which should be evaluated further. ***Cancer*** **2008;112:1600–6.** © *2008 American Cancer Society.*

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Painful sores and ulcers in the lining of the mouth (oral mucositis [OM]) are common complications to some chemotherapy regimens. The incidence varies, depending on the chemotherapy agent used, doses, and schedules. It is a well-known frequent complication of high-dose chemotherapy but also occurs with some chemotherapy regimens applied in conventional dosing. Administration of bolus infusions of 5-fluorouracil (5-FU), with or without leucovorin, has been associated with OM in 40% of patients.[1,2] Grade 3–4 OM approached 14% among 3177 patients in 21 studies using 5-FU.[3]

Patients suffering from the complication have difficulty eating and swallowing. In the most severe form of OM, patients cannot eat

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or drink at all and must receive nutrition and fluid replacement through parenteral or enteral support. OM in neutropenic patients may also represent a clinically significant risk factor for sepsis.[3] Furthermore, it may in some patients be a dose-limiting toxicity, delaying or preventing continuation of chemotherapy,[3] which may potentially have an impact on survival or even cure, eg, in completely resected colon cancer patients receiving adjuvant 5-FU-based treatment.

Topical cooling of the oral mucosa (cryotherapy) may be an option in the prevention of OM.[4] The theoretical rationale for this approach is that cryotherapy leads to vasoconstriction and decreased blood flow to the oral cavity, which reduces the exposure of the buccal mucosa to chemotherapy. Because 5-FU has a short half-life of around 20 minutes, oral cooling for 30 to 45 minutes immediately before and after chemotherapy administration may reduce the frequency of OM, as suggested in previous randomized trials.[5–7]

The influence of indigenous normal oral flora on OM has not been clearly delineated, but these organisms have been implicated as a potential contributing factor in the complex pathway leading to mucosal barrier injury.[3] During the ulcerative phase of mucositis, bacterial colonization occurs with Gram-positive, Gram-negative, and anaerobic organisms. The role of such oral environmental factors as bacteria and their products are unclear[3] but have been the rationale for involving antimicrobial mouth rinse using chlorhexidine for prophylactic effects. An early randomized study by Feretti et al.[8] using chlorhexidine prophylactic mouthrinse reported on reduced frequency and severity of OM, whereas later trials have shown the effect of directly reducing the bacterial load on the course of mucositis to be erratic.[9]

On this background it was of interest first to elucidate whether prophylactic mouth rinse using Chlorhexidine has a role or not in prevention of chemotherapy-induced OM, second to evaluate whether it is superior or not to the oral cooling (Cryotherapy). Thus, these 2 preventive measures were to be compared with respect to the incidence, severity, and duration of OM in patients treated with 5-FU bolus chemotherapy. The 2 prophylactic measures were chosen to be compared with simple mouth rinse using normal saline to verify a prophylactic effect of the interventional regimens.

MATERIALS AND METHODS

Patients

Eligible patients had either gastric or colorectal cancer and were to receive 5-FU containing chemotherapy according to the Mayo regimen. All were chemotherapy naive, had a healthy oral mucosa and signed informed consent. Exclusion criteria included a history of head and neck radiotherapy, and symptoms of any infections. The dental status had to be sufficient good to allow for cryotherapy with crushed ice without dental complains, ie, the patients had no history of dental-or mouth discomfort related to cold or hot food or beverage intake. Complete or partial dental prosthesis was allowed.

Patients gave informed consent after verbal and written information. The study was conducted according to the Helsinki declaration and was approved by the local Ethical Committees.

Chemotherapy

The antineoplastic treatment was according to the Mayo regimen using bolus infusion of 5-FU.[6] Leucovorin 20 mg/m^2 bolus infusion was followed by bolus infusion of 5-FU 425 mg/m^2 daily in 5 days every 4 weeks.

Study Design

Patients were stratified according to age ($<$40 vs $\geq$40 years), smoking habit (yes vs no), and the use of dental prosthesis (yes vs no), and randomized after informed consent to 1 of 3 prophylactic regimens (Arm A: chlorhexidine mouthwash; Arm B: placebo mouthwash [normal saline]; Arm C: crushed ice [cryotherapy]). Both patients and physicians were blinded with respect to the content of the fluid for mouthwash in Arm A and B, which were packed in identical 500-mL bottles labeled "X" and "Y,", respectively.

The effect of the prophylactic intervention was evaluated after the first treatment course at the time when patients came for the start of the second course on Day 28. Patients self-evaluated severity and duration of OM together with side effects on a questionnaire on Days 14 and 28 and were instructed to observe and register signs and symptoms from the oral cavity on a daily basis and write it into the questionnaires Day 14 and 28. The treating physician made assessment of CTC mucositis grade during the visit Days 14 and 28 in the first treatment course. The patients assessment was the chosen endpoint in the study because many of the items in the CTC scale per se are dependent on the patients' subjective registration, eg, items such as soreness or painful erythema. NCI-CTC grading v. 2.0 of OM was used. The patients used a similar translation to Danish of the grading system as the physicians, neither of which are validated.

TABLE 1
Characteristics of 206 Patients Randomized in the 3-Arm Double-Blind Study of Oral Mucositis Prophylaxis

	Arm A No. (%)	Arm B No. (%)	Arm C No. (%)	Total No. (%)
Total	73	66	67	206
Diagnosis				
CRC Dukes BC	63 (86)	56 (85)	54 (81)	173 (84)
CRC Dukes D	6 (8)	7 (11)	10 (15)	23 (11)
Gastric cancer	4 (5)	3 (4)	3 (4)	10 (5)
Sex				
Men	39 (53)	35 (53)	40 (60)	114 (55)
Women	34 (47)	31 (47)	27 (40)	92 (45)
Age, y				
<40	6 (8)	3 (5)	2 (3)	11 (5)
≥40	67 (92)	63 (95)	65 (97)	195 (95)
Median [range]	62 [28–82]	61 [30–81]	62 [36–84]	62 [28–84]
Smoker				
No	52 (71)	46 (70)	48 (72)	146 (71)
Yes	21 (29)	20 (30)	19 (28)	60 (29)
Performance status				
0	65 (89)	59 (89)	62 (93)	186 (90)
1	7 (10)	7 (11)	4 (6)	18 (9)
2	1 (1)	0	1 (1)	2 (1)

CRC indicates colorectal cancer; Arm A, chlorhexidine mouth wash; Arm B, placebo mouthwash (normal saline); Arm C, cryotherapy (oral cooling).

Also, hematologic toxicity was registered with blood samples on Days 14 and 28. Patients were allowed to continue 1 of each of the 3 prophylactic regimens according to their own choice from the second chemotherapy course onwards, but the results of this were not recorded as it was outside the scope of this study.

Oral Mucositis Prophylaxis

The prophylaxis in Arm A was chlorhexidine 0.1% mouthwash 10 mL and the patients swirled it around in the mouth for 1 minute 3 times a day, Days 1–21. It was without alcohol and with taste additives. The constituent of the placebo in Arm B was normal saline with the same taste additives as in Arm A, and with the same mouthwash schedule.

Patients used cryotherapy with crushed ice in the mouth from 10 minutes before until 35 minutes after the start of each chemotherapy infusion in Arm C. Patients were instructed in all cases to remove prosthesis, if relevant, before the prophylactic procedures. Furthermore, they were instructed to continue prophylaxis in case OM occurred, which was treated according to the discretion of the respective investigators. Ice-machines were cleaned every week according to a standardized concept and no contamination of the machines has occurred.

TABLE 2
Side Effects and Compliance of the Prophylactic Regimens for Oral Mucositis

	Arm A, n = 73 No. (%)	Arm B, n = 66 No. (%)	Arm C, n = 67 No. (%)
Taste disturbance			
No	38 (52)	41 (62)	43 (64)
Yes	35 (48)	25 (38)	24 (36)
Headache			
No	63 (86)	57 (86)	53 (79)
Yes	10 (14)	9 (14)	14 (21)
Compliance			
Complete	55 (75)	53 (80)	58 (87)
Partial	18 (25)	13 (20)	9 (13)

Arm A indicates chlorhexidine mouthwash; Arm B, placebo mouthwash (normal saline); Arm C, cryotherapy (oral cooling).

Statistical Methods

A 15% decrease in the incidence of CTC grade 3–4 OM was considered clinically meaningful. With a 2-sided type I error of 5% and a type II error of 20% it was calculated that 75 patients were to be randomized in each arm for a total of 225 patients. Chi-square tests were used for comparison of proportions and the Mann-Whitney rank sum test for comparison of continuous data.

RESULTS

Patient Characteristics

A total of 225 patients were randomized from 2001 to 2005, with 75 in each of the prophylactic arms. However, not all patients returned the questionnaire on side effects and compliance, leaving 206 evaluable patients for analysis, including 73, 66, and 67 patients in Arms A, B, and C, respectively (Table 1). The characteristics with respect to diagnosis, sex, age, smoking habits, and performance status were equally distributed between the prophylactic arms. Most patients had completely resected colon or rectal cancer Dukes B or C (84%) and most had performance status 0 (90%). Only 11 patients were below 40 years of age (5%), all 3 arms included patients above 80 years, and the median ages were similar, being 61 to 62 years (Table 1). Similarly, there were no differences in total leukocyte count nadirs during the first course of chemotherapy.

Compliance and Side Effects of Prophylactic Regimens

No statistically significant differences occurred with respect to compliance to the prophylactic regimens or to side effects such as headache or taste disturbances (Table 2). No effects on teeth were registered.

TABLE 3
CTC Grading and Duration of Oral Mucositis During First Chemotherapy Course

		Arm A Clhex, n = 73 No. (%)	Arm B Plac, n = 66 No. (%)	Arm C Cryo, n = 67 No. (%)
CTC grade	0	31 (43)	15 (23)	29 (43)
	1	19 (26)	18 (27)	18 (27)
	2	11 (15)	10 (15)	9 (13)
	3	8 (11)	21 (32)	7 (10)
	4	1 (1)	0	0
	NA	3 (4)	2 (3)	4 (6)
CTC grade 3+4	*P* vs placebo	<.01		<.005
Duration of OM	No OM	30 (41)	15 (23)	30 (45)
	OM 1–7 d	24 (33)	30 (46)	24 (36)
	OM > 7 d	18 (25)	18 (27)	10 (15)
	Median [range]	3 d [0–17]	5 d [0–20]	1 d [0–20]
	P vs Arm B	.035		.003

CTC indicates Common Toxicity Criteria; OM, oral mucositis; Arm A, chlorhexidine mouthwash; Arm B, placebo mouthwash (normal saline); Arm C, cryotherapy (oral cooling).

A trend toward better compliance with Arm C was observed, with a complete compliance rate of 87% as compared with 75% and 80% in Arms A and B, respectively. There was a trend toward more patients complaining of headache in Arm C (21%) compared with the 14% each in Arms A and B, and more complaints of taste disturbances in Arm A (48%) compared with Arms B (38%) and C (36%).

Grading and Duration of OM

Only 23% of patients in Arm B did not experience any grade of OM, whereas this was the case for 43% in both Arms A and C (Table 3). Only 1 patient in the entire population had grade 4 OM, being in Arm A. The frequency of grades 3 or 4 OM were 12%, 32%, and 10% in Arms A, B, and C, respectively. This frequency was significantly lower in both Arm A ($P < .01$) and Arm C ($P < .005$) when compared with Arm B, whereas Arms A and C were similar. There were no significant differences between the patients or the treating physicians scoring of mucositis severity.

The median durations of OM in Arms A, B, and C were 3 days, 5 days, and 1 day, respectively. It was significantly shorter than Arm B in both Arm A ($P = .035$) and Arm C ($P = .003$). There was no difference between Arms A and C.

Predictors of OM

Neither smoking habits nor performance status predicted severity of OM. With respect to age, only 11 patients were younger than 40 years of age, which hampers statistical power. However, among these 11 young patients 4 had OM grade 3 or 4 (36%) as compared with 33 of 195 older patients (17%). This difference was not statistically different ($P = .14$).

DISCUSSION

Most data on the incidence of OM are derived from clinical trials of chemotherapy regimens in which reporting of toxicity is a secondary objective and the frequencies reported may thus be minimum figures. A recent review of the occurrence of OM found, not unexpectedly, that virtually all trials were underpowered and unable to produce stable estimates of toxicity.[3] The incidence of OM varied significantly among different drugs and treatment regimens. The overall OM rate of any grade with 5-FU treatment has previously been reported to be around 40%,[1,2] whereas administration of bolus 5-FU with leucovorin were confined with grade 3–4 OM in 14% of totally 3177 patients (95% confidence limits [CL], 12%–15%) and continuous infusion of 5-FU in 146 patients had a similar 14% grade 3–4 OM rate (95% CL, 10%–18%).[3]

The 62% overall rate of OM reported in this study is somewhat higher than previous reports. Also, grade 3–4 OM were somewhat more frequent than expected, being 32% in patients receiving placebo mouthrinse in Arm B, whereas the overall rate of 18% (95% CL, 13%–24%) in the entire study population are close to the figures reported in a review by Sonis et al.[3] A probable explanation for the trend toward higher frequencies of OM in this study might be that it was the major endpoint in the study, so that underreporting is less likely, and also the finding that the figures are based on patient self-reported toxicity may have had an influence. It is clear from a

previous report on patient perceptions about chemotherapy-induced OM that this toxicity is considered very troublesome by the patients.[10] Among 167 patients (32%) who reported experiencing OM of 514 patients in the analysis, 69% considered it to be an important toxicity and OM was considered the sixth most distressing complication behind (in descending order) fatigue, hair loss, nausea, numbness, and diarrhea.[10]

Cryotherapy was significantly better than mouthrinse with normal saline (arm B) in this study, both with respect to severity ($P < .005$) and duration ($P = .003$). This is in accordance with several other randomized trials evaluating the effect of cryotherapy prophylaxis with bolus 5-FU according to the Mayo regimen[5,6] or with other cytotoxic agents,[11,12] although not all studies revealed a significant advantage for cryotherapy.[13] A recent metaanalyses[14] also found that cryotherapy prevented OM at all levels of severity with risk ratios from 0.27 (95% CL, 0.11–0.68) to 0.63 (95% CL, 0.44–0.91).

It is interesting that the current study showed superiority of cryotherapy compared with the standard arm (Arm B) although Arm B was not a no-treatment arm but consisted of normal saline mouthrinse 3 times a day. Oral care has previously documented in different randomized trials with various oral care programs to have a beneficial effect on OM in 3 studies[15–17] and only 1 study reported no effect.[18] Thus, Arm B in this study cannot be considered a no-treatment arm. Although the effect of cryotherapy in this setting may now be concluded to be firmly established, this prophylactic concept has some important limitations. It counts on the positive side that it is cheap, readily available, and without severe side effects. However, its use is very drug- and schedule-dependent. It is limited to prophylactic use with cytostatic agents like 5-FU with a very short half-life and to the use of such agents with bolus or very short-term infusions. Although 5-FU is a cornerstone of treatment for colorectal cancer, the most active regimens are now using continuous infusion, which is confined with a better efficacy and better toxicity profile.[19,20] This narrows down the areas of use for this concept, but it remains of important value in a few cytostatic regimens using bolus 5-FU and in dose-dense chemotherapy regimens, eg, such as a recently reported positive effect in high-dose melphalan in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation.[13,21]

The situation with respect to the role of chlorhexidine is less clear. This may partly be because of the various clinical scenarios in which it has been tested. This includes both prevention and treatment of OM, different treatment modalities such as radiation or chemotherapy, various cytostatic agents with different potentials for inducing OM, conventional and high-dose chemotherapy regimens, and various patient populations such as adults with solid tumors, hematologic malignancies, or pediatric patients. Also, the variability of the mouthrinse regimens with respect to dose, frequency, and duration may contribute to disparity, together with the often extremely small sample sizes, making type 2 errors likely to occur. The use of patient self-scored evaluation is in accordance with other recent trials of OM.[12,13]

It is a consistent finding from 3 randomized trials that chlorhexidine has no impact in preventing[22,23] or treating[24] OM in patients with solid tumors of the head and neck undergoing radiotherapy. Likewise, in chemotherapy-induced OM chlorhexidine has failed to be beneficial as a treatment for established OM in 3 trials.[25–27] Both of these situations are described in the recently updated guidelines from the Multinational Association of Supportive Care in Cancer (MASCC), which also find no indications for chlorhexidine as prevention of chemotherapy-induced OM, either in adults or in the pediatric situation.[28] The latter statement, however, may be somewhat modified in the light of this study and also other recent trials. Conflicting results have been reported in older randomized prevention trials with both positive and negative reports, eg, such as the trials by Ferretti et al.[8] and Dodd et al.,[29] respectively. These studies share common methodological problems such as low sample sizes or various chemotherapy agents confined with a high and low mucositis-inducing capacity used within the same study. It is, however, interesting that the trial by Ferretti et al.[8] was double-blinded and reported a significant reduction of incidence ($P < 0.002$) and severity ($P < 0.03$) of OM among 40 randomized patients receiving chemotherapy. Also, a newer unblinded study by Luglie et al.[30] in 63 patients receiving 5-FU-based chemotherapy observed a lower incidence of OM in the group allocated to chlorhexidine as compared with controls, being 20% versus 66%, respectively ($P < 0.05$). Cheng et al.[31] compared 2 protocols of oral care using either chlorhexidine or benzydamine mouthrinse to alleviate OM in 40 children undergoing chemotherapy using regimens including 5-FU, doxorubicin, or methotrexate. A statistically significant reduction in ulcerative lesions ($P < 0.05$) and severity of OM ($P < 0.05$) in children on the chlorhexidine prophylaxis was reported. The study was not blinded.

The findings in the 3 latter trials[8,30,31] correspond well with the findings in this study, which, however,

is the first double-blind, randomized evaluation of chlorhexidine in a large patient population treated homogeneously with a single chemotherapy regimen of highly mucositis-inducing potential. As such, the results may indicate that chlorhexidine has a role for prevention of OM in adult patients with solid tumors treated with chemotherapy in conventional doses. The price based on drug costs in Denmark equals about €50 per treatment course lasting 3 weeks. It may be hypothesized that the use of chlorhexidine mouthrinse using an alcohol mixture may contribute to the lack of effect or even harmful effect in some radiation prophylactic trials but firm conclusions cannot be drawn because of a lack of information on the interventional formulation (ie, with alcohol or not) in the reports. The current study cannot directly address this question but may suggest that a solution without alcohol should be preferred, such as used in this study.

Clearly, this study could not be blinded in the comparison to cryotherapy. Identical taste corrigents were used in the chlorhexidine and in the placebo arm and no obvious reason for this blinding not to hold is encountered. However, as this was not a crossover design, no patients have tried both chlorhexidine and placebo, for which reason it is impossible to completely rule out that a difference in taste can be detected by the patients. Chlorhexidine does not have the disadvantage of being restricted to use with chemotherapy agents with a short half-life, such as is the case for cryotherapy. However, the results may not immediately be extrapolated to other patient populations such as hematologic malignancies or children, nor to other chemotherapy scenarios such as high-dose treatments in relation to stem cell transplant programs. These situations may be the subject of further investigations.

A new treatment concept using Palifermin (rHu-KGF1), a keratinocyte growth factor receptor antibody, is now registered for prevention of OM in the autologous hematopoietic stem-cell transplantation (HSCT) setting for hematologic cancers based on a study by Spielberger et al.[32] The activity of Palifermin in the HSCT setting was further supported by the findings in 212 hematologic cancer patients randomized to Palifermin or placebo in a recent trial by Stiff et al.[33] A statistically significant improvement of patient self-reported OM was observed. In contrast to hematologic cancers, some epithelial malignancies carry keratinocyte growth factor receptors, and there is thus a potential risk for the stimulation of epithelial tumor growth. One recent randomized trial among 64 patients with metastatic colorectal cancer receiving fluorouracil/leucovorin bolus chemotherapy revealed statistically significant reduction of OM grade 2 or worse from 62% in the placebo group to 29% in the Palifermin group ($P = 0.016$).[34] No differences in overall survival time or progression-free survival were noted but the study was not powered to detect such differences. Additional studies are needed to evaluate fully the long-term safety of Palifermin in the solid tumor setting.

In conclusion, the frequency and duration of OM may be significantly improved by either prophylactic chlorhexidine or by cryotherapy. The latter is easy and inexpensive but is drug- and schedule-dependent, as it cannot be used with infusional 5-FU or with chemotherapy with substantially longer half-lives than 5-FU. The current study is the first double-blind, randomized evaluation of chlorhexidine in a large patient population treated homogeneously with a single chemotherapy regimen of highly mucositis-inducing potential. The results point toward a role for chlorhexidine in the prevention of OM in adult patients with solid tumors treated with chemotherapy in conventional doses, without having the disadvantage of being restricted to use with chemotherapy agents with a short half-life, such as is the case for cryotherapy. Whether chlorhexidine is as effective as Palifermin remains to be evaluated.

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