Prospective Evaluation of a Chamomile Mouthwash for Prevention of 5-FU-Induced Oral Mucositis

Pat Fidler, R.N.[1]
Charles L. Loprinzi, M.D.[2]
Judith R. O'Fallon, Ph.D.[2]
John M. Leitch, M.D.[3]
Jeraldine K. Lee, R.N.[2]
Debra L. Hayes, R.N.[4]
Paul Novotny, M.S.[2]
Danette Clemens-Schutjer, R.N.[5,6]
Joan Bartel, R.N.[7]
John C. Michalak, M.D.[8]

[1] Nebraska Oncology Group, Creighton University, University of Nebraska Medical Center, and Associates, Omaha, Nebraska.

[2] Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

[3] Meritcare Hospital CCOP, Fargo, North Dakota.

[4] Illinois Oncology Research Association Community Clinical Oncology Program, Peoria, Illinois.

[5] Iowa Oncology Research Association Community Clinical Oncology Program, Des Moines, Iowa.

[6] Mercy Cancer Center, Mason City, Iowa.

[7] Saskatchewan Cancer Foundation, Allan Blair Memorial Clinic, Regina, Saskatchewan CANADA.

[8] Siouxland Hematology-Oncology Associates, Sioux City, Iowa.

This study was conducted as a collaborative trial of North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service grants CA-25224, CA-37404, CA-15083, CA-37417, CA-35113, CA-35101, CA-52352, CA-35415, CA-35195, CA-35103, CA-35448, and CA-35269 from the National Cancer Institute, Department of Health and Human Services.

Address for reprints: Charles L. Loprinzi, M.D., Mayo Clinic, 200 First Street, SW, Rochester, MN 55905.

Received June 19, 1995; revision received September 22, 1995; accepted September 22, 1995.

BACKGROUND. Stomatitis has been found to be a major dose-limiting toxicity from bolus 5-fluorouracil-based (5-FU) chemotherapy regimens, despite the use of oral cryotherapy. Pursuant to preliminary data which suggested that a chamomile mouthwash might ameliorate this toxicity, a prospective trial was developed to test chamomile in this situation.

METHODS. A Phase III, double-blind, placebo-controlled clinical trial was designed. Patients were entered into the study at the time of their first cycle of 5-FU-based chemotherapy. All patients received oral cryotherapy for 30 minutes with each dose of 5-FU. In addition, each patient was randomized to receive a chamomile or placebo mouthwash thrice daily for 14 days. Stomatitis scores were determined by health care providers and by patients themselves.

RESULTS. There were 164 evaluable and well-stratified patients equally randomized to both treatment groups. There was no suggestion of any stomatitis difference between patients randomized to either protocol arm. There was also no suggestion of toxicity. Subset analysis did reveal unsuspected differential effects between males and females that could not be explained by reasons other than chance.

CONCLUSION. The resultant data from this clinical trial did not support the prestudy hypothesis that chamomile could decrease 5-FU-induced stomatitis. ***Cancer* 1996; 77:522–5.** © *1996 American Cancer Society.*

KEYWORDS: mucositis, stomatitis, chamomile, symptom-control study, chemotherapy toxicity.

Stomatitis is one of the dose-limiting toxicities of 5-fluorouracil (5-FU). While rarely life threatening, the oral discomfort of ulcerations produced by 5-FU can be very painful and may influence patient compliance with future cytotoxic therapy. Severe ulceration of the mouth and gastrointestinal tract can significantly interfere with nutrition and may result in oral or systemic infection. Currently, no successful intervention exists to prevent stomatitis completely. Any measure to alleviate or decrease the frequency and/or severity of stomatitis would be of obvious benefit. It may also allow a greater opportunity for tumor response if higher doses of chemotherapy could be safely given.

A previously-reported randomized trial of oral cryotherapy for 30 minutes versus control in patients receiving 5-FU plus leucovorin demonstrated impressively less stomatitis in patients randomized to cryotherapy.[1] A subsequent trial failed to demonstrate additional benefit by increasing the oral cryotherapy duration to 60 minutes.[2] Despite the use of cryotherapy, stomatitis continues to be a prominent clinical problem affecting approximately 40% of patients receiving 5-FU-based chemotherapy.[1,2] Thus further efforts are warranted to attempt to decrease 5-FU-related stomatitis.

TABLE 1
Distribution of Baseline Factors in Randomized Patients

Baseline factors	Chamomile (n = 82)	Placebo (n = 82)	*P*-Value
Denture wearer			0.99[a]
Yes	35%	34%	
No	65%	66%	
Current smoking history			0.51[a]
None	88%	87%	
Cigarette	12%	10%	
Pipe or cigar	0%	2%	
Smokeless tobacco	0%	1%	
Chemotherapy regimen			0.99[a]
5-FU 425 mg/d + CF 20 mg/d	13%	12%	
5-FU 370 mg/d + LCF 100 mg/d	16%	15%	
5-FU 370 mg/d + CF 500 mg/d	21%	20%	
5-FU 370 mg/d + CF 200 mg/d	18%	20%	
5-FU 370 mg/d + CF 20 mg/d + LEV	32%	34%	
5-FU 425 mg/d + CF 20 mg/d + LEV	0%	0%	
Sex			0.34[a]
Female	48%	39%	
Male	52%	61%	
Age			0.78[b]
Mean	64.3	63.4	
Median	65.5	65.5	
Condition of teeth and gums			0.99[a]
Good	88%	88%	
Fair	11%	11%	
Poor	1%	1%	

5-FU: 5-fluorouracil; CF: citrovorum factor (leucovorin); LCF: l-isomer of leucovorin; LEV: levamisole; [a]: Chi-squared test; [b]: Wilcoxon rank sum test.

TABLE 2
Distribution of Efficacy Measures by Arm

Efficacy Variables	Chamomile	Placebo	*P*-Value*
Physician-judged	(n = 82)	(n = 82)	0.43
Maximum severity of stomatitis			
None	60%	55%	
Mild	26%	22%	
Moderate	5%	15%	
Severe	6%	7%	
Very severe	4%	1%	
Mean	0.85	0.94	
Patient-judged	(n = 70)	(n = 65)	0.32
Maximum severity of stomatitis			
None	51%	39%	
Mild	27%	40%	
Moderate	9%	14%	
Severe	10%	5%	
Very severe	2%	3%	
Mean	1.0	1.2	
Duration of stomatitis	(n = 34)	(n = 40)	0.85
Median	8 days	9 days	

* Wilocoxon rank sum test.

The chamomile plant has been used for medicinal purposes for centuries.[3,4] This plant contains many different substances including chamazulene, alpha bisabolol, bisabolol oxides, spiroethers, and flavenoids. Data suggest that these compounds have anti-inflammatory, antibacterial, and antifungal properties.[3–6] A pilot study suggested that chamomile might be helpful in patients with inflammatory conditions of the oral cavity.[7] Such information led investigators to study chamomile as an oral rinse in 98 cancer patients receiving chemotherapy or radiation therapy.[8] Some of the patients studied by these investigators received chamomile therapeutically while others received it prophylactically. These investigators reported that the chamomile was well tolerated without any noted toxicity in their patients. The investigators felt that the data from their uncontrolled trial supported the contention that chamomile could decrease stomatitis in cancer patients. To study this contention in a definitive manner, the following clinical trial was designed.

MATERIALS AND METHODS

Patients considered for this study must have been scheduled to receive their first course of a 5-FU-based, five consecutive day chemotherapy regimen on a North Central Cancer Treatment Group (NCCTG) cancer treatment protocol. They were stratified for whether or not they wore dentures, their smoking history, the institution where they were randomized, and the chemotherapy regimen which they received. Following informed consent, they were randomized in a double-blind manner to receive a chamomile mouthwash or an identical-appearing placebo.

Before initiation of chemotherapy, patients were asked to remove their dentures. They were instructed to place ice chips in their mouth five minutes before each dose of 5-FU, continuously swish the ice around inside their mouths, and replenish the ice chips before the previous ice had completely melted. This was done for a total of 30 minutes.

The chamomile/placebo was administered 3 times daily for 14 days starting on the first day of chemotherapy. To take this, patients measured 100 mL of water and added 30 drops of a concentrated chamomile/placebo agent. This solution was swished around in the mouth for approximately one minute and then expectorated. This was repeated 3 to 5 times until the entire 100 mL was used. This chamomile preparation was chosen based on the available pilot data.[7] The chamomile was provided by ASTA Medica, Incorporated (Hackensack, NJ).

Stomatitis scores were determined by the attending physicians in the manner commonly utilized in cancer clinical trials. The score was generally judged by historical means four to five weeks after chemotherapy cycle initiation. The scores were graded from 0 to 4 (0 = none, 4 =

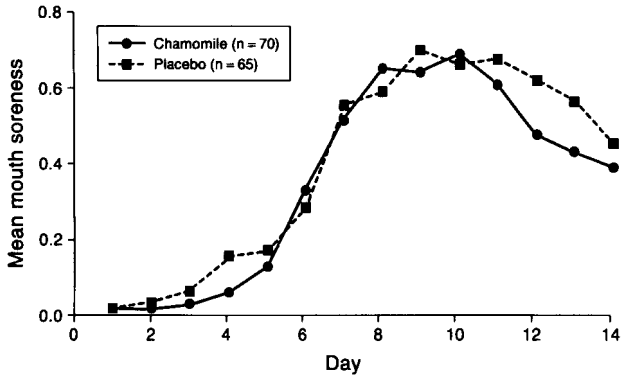

FIGURE 1. Daily mean mucositis scores for the two study arms (P = 0.32).

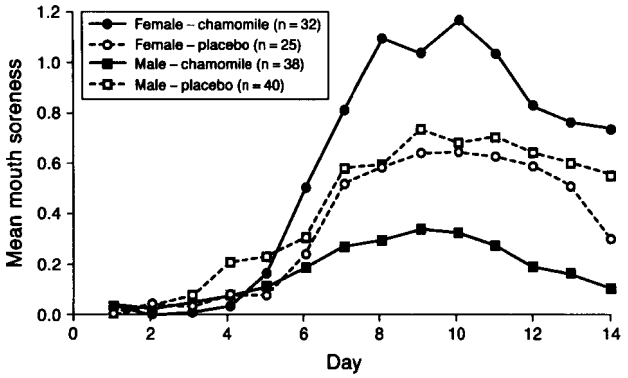

FIGURE 2. Daily mean mucositis scores for the two study arms grouped by gender.

most severe) as per previous studies.[1,2,9] Additionally, a patient-completed form was developed based on the same toxicity scores. This questionnaire was given to the patients by their oncology nurse at the time of study entry and was filled out by the patients on a daily basis for three weeks after the first day of chemotherapy. This questionnaire was a modification of questionnaires used in three previous trials.[1,2,9]

The original accrual goal for this study was 160 evaluable patients. With this sample size it was calculated that a one-sided, 0.025-level Wilcoxon test would have approximately 90% power to detect clinically appropriate stomatitis differences in the scores between the chamomile and placebo groups. A planned interim analysis was to be done after approximately half of the patients had been entered in the study.

RESULTS

Between October 1991 and January 1994, 165 patients were randomized. One patient was removed from the analysis because of a major protocol violation. The 164 evaluable patients were evenly randomized between the two study arms. The two treatment groups were well balanced on all evaluated pretreatment variables (Table 1).

Protocol entry was temporarily stopped and a planned interim analysis was done after 80 patients had been entered into this trial. This analysis indicated that it was appropriate to reopen accrual to meet the original goal.

All of the 164 patients had evaluable physician-judged stomatitis severity data. However, 12 of the chamomile patients (15%) and 17 of the placebo patients (21%) did not provide enough information to be evaluable for patient-reported efficacy. Table 2 and Figure 1 illustrate that there was no substantial difference in stomatitis scores between the two protocol arms. While these data do not convincingly rule out the possibility that chamomile might have a small beneficial effect, the 95% confidence interval for differential mucositis scores between the chamomile and placebo arms is −23% and +15%.

An exploratory subset analysis based on gender revealed surprising results which suggest that chamomile might be beneficial for males and detrimental for females (Fig. 2). Detailed multivariate analysis identified both a significant chamomile effect and a gender interaction with chamomile, even after adjusting for the effects of the stratification factors and baseline descriptive factors. No biologically plausible explanation for these results was found. Moreover, the hypothesis that men and women might have different scoring patterns seemed belied by the strikingly similar scoring patterns of the men and women who received placebo.

There was no evidence that chamomile caused any toxicity. Specifically, there was no suggestion of a differential incidence of nausea, vomiting, anorexia, dysphagia, diarrhea, or constipation between the two study arms.

DISCUSSION

The results from this trial were unable to support the prestudy hypothesis that chamomile can lessen 5-FU-induced mucositis. The differential results in males and females were unexpected and remain unexplained. It is most probable that they occurred by chance, as subset analyses have a well-understood potential to produce spurious results. Thus, confirmatory evidence is necessary to validate a differential therapeutic effect according to gender.

At the present time it is recommended that the use of 30 minutes of oral cryotherapy for prophylaxis of bolus dose, 5-FU-based chemotherapy be continued.[1] To date, no other effective measure has been proven to be useful for this problem.

Further studies are indicated to try to find new methods to decrease 5-FU-induced mucositis. Agents worthy

of evaluation include sucralfate,[10,11] vitamin E,[12,13] glutamine,[14,15] and nonabsorbable antibiotic lozenges.[16,17] Cooperative oncology group studies are in process to evaluate these possible remedies.

ACKNOWLEDGMENTS

Additional participants include: Martin Wisenfeld, M.D., Cedar Rapids Oncology Project CCOP, Cedar Rapids, IA; Paul L. Schaefer, M.D., Toledo Community Clinical Oncology Program, Toledo, OH; Alan K. Hatfield, M.D., Carle Cancer Center Community Clinical Oncology Program, Urbana, IL; Loren K. Tschetter, M.D., Sioux Community Cancer Consortium, Sioux Falls, SD; Suresh Nair, M.D., Geisinger Clinical Oncology Program, Danville, PA; Ron J. Kirschling, M.D., Duluth Community Clinical Oncology Program, Duluth, MN; Larry P. Ebbert, M.D., Rapid City Regional Oncology Group, Rapid City, SD; Delano M. Pfeifle, M.D., Quain and Ramstad Clinic, Bismarck, ND; Harold E. Windschitl, M.D., CentraCare Clinic, St. Cloud, MN; Donald I. Twito, M.D., Billings Clinic, Billings, MT; John A. Laurie, M.D., Grand Forks Clinic, Ltd., Grand Forks, ND.

REFERENCES

1. Mahood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Therneau TM, et al. Inhibition of 5-fluorouracil-induced mucositis by oral cryotherapy. *J Clin Oncol* 1991;9:449–52.
2. Rocke LK, Loprinzi CL, Lee JK, Kunselman SJ, Iverson RK, Finck G, et al. A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. *Cancer* 1993;72(7):2234–8.
3. Isaac O. Advances in chamomile research. *Deutsche Apotheker-Zeitung* 1974;114(7):155–260.
4. Craker LC and Simon JE. Herbs, spices, and medicinal plants: recent advances in botany, horticulture, and pharmacology. vol. 1 Oryx Press, 1986.
5. Aggag ME and Yousef RT. Study of antimicrobial activity of chamomile oil. *PLMEAA* 1972;22(2):109–212.
6. Della Loggia R. Topical anti-inflammatory action of the chamomile flovones. *Duetsche Apotheker-Zeitung*, (I Suppl):9–11.
7. Klaschka F, Maiwald L, Patzelt-Wenczler R. Chamomile: mode of action and formulations. Interdiscipolinary Chamomile Symposium; 1987; Frankfurt/Main, West Germany.
8. Carl W, Emrich LS. Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. *J Prosthet Dent* 1991;66:361–9.
9. Loprinzi CL, Cianflone SG, Dose AM, Etzell PS, Burnham NL, Therneau TM, et al. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. *Cancer* 1990;65(8):1879–82.
10. Ferrara JM, Mattern JQU II. Sucralfate suspension for stomatitis [letter]. Drug Intelligence and Clinical Pharmacy 1984;18:153.
11. Shenep JL, Kalwinsky DK, Hutson PR, George SL, Dodge RK, Blonkenship KR, et al. Efficacy of oral sucralfate suspension in prevention and treatment of chemotherapy-induced mucositis. *J Pediatr* 1988;4:113,758–63.
12. Wadleigh R, Redman R, Cohen M, Krasnow S, Anderson A, Graham M. Vitamin E in the treatment of chemotherapy-induced mucositis. *Proc ASCO* 1990;9:1237.
13. Kim JE, Shklar G. The effect of vitamin E on the healing of gingival wounds in rats. *J Periodontol* 1983;54:305–8.
14. Anderson PM, Skubitz KM. Oral glutamine suspension to ameliorate chemotherapy induced mucositis [abstract]. ASPHO Proc 1993;2:32.
15. Fox AD, Kripke SA, De Paula J, Berman JM, Settle RG, Rombeau JL. Effect of a glutamine-supplemented enteral diet on methotrexate-induced enterocolitis. *J Parenter Enter Nutr* 1988;12(4):325.
16. Spijkervet F, Vermey A, Panders A, Saene H, Mehta D. Prevention of irradiation mucositis in head-neck cancer patients. *Proc ASCO* 1990;9:174.
17. Kaanders JHAM, Pop LAM, Uitterhoeve RJ, van Daal WAJ. Prevention of irradiation mucositis in the oral cavity and oropharynx by PTA-lozenges. *Int J Radiat Oncol Biol Phys* 1993;1 Suppl 27:253.