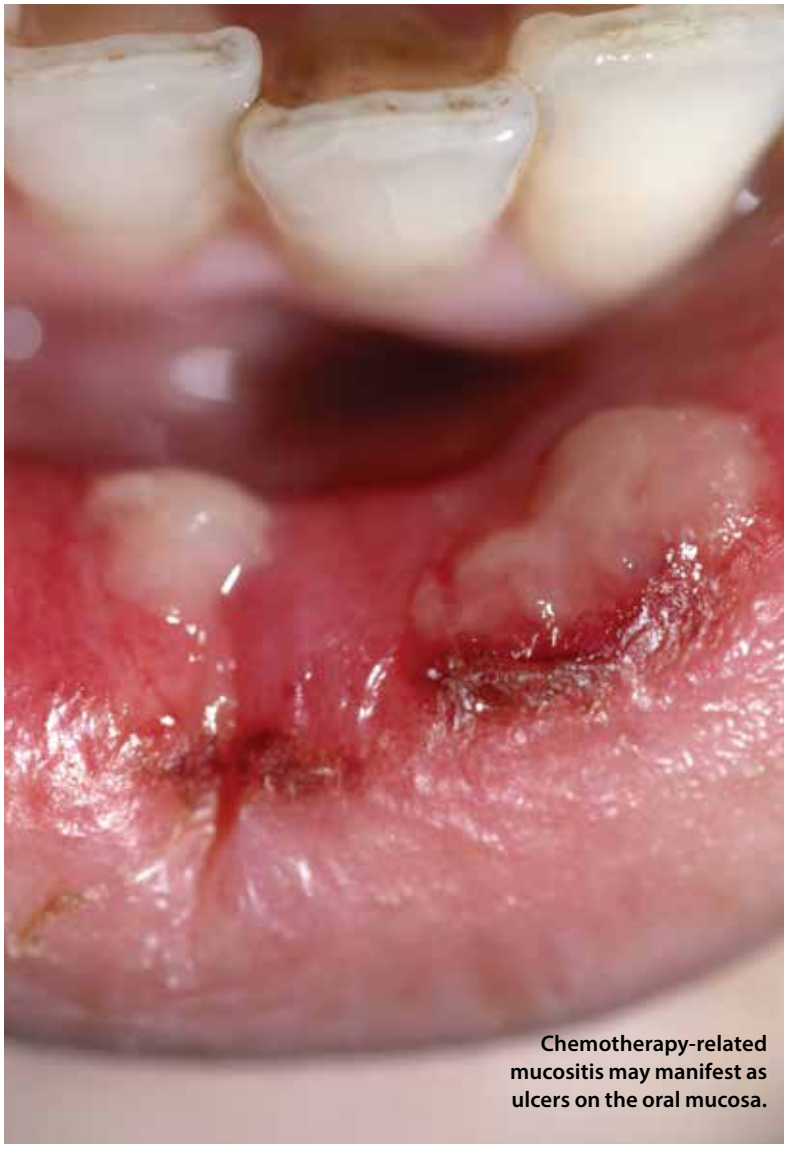
Easing the effects of radiation therapy to the head and neck

A clinical evaluation demonstrates the effectiveness of a mucoadhesive polymer rinse on oral mucositis, a common side effect of radiotherapy



Chemotherapy-related mucositis may manifest as ulcers on the oral mucosa.

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Oral mucositis (OM) is a debilitating side effect of cancer therapy that can have a significant negative impact on health, quality of life, and treatment outcomes. Occurrence leads to dose reductions, delay in cancer therapy, discontinuation of therapy, and hospitalizations. Almost all patients with head and neck cancer who undergo radiation/chemoradiation develop some grade of oral toxicity and pain.[1] An estimated 40% or more of cancer patients undergoing chemotherapy will experience OM, and incidence among patients who receive high doses of chemotherapy during bone marrow transplantation is 76%.[2-4] Oral mucositis poses a significant challenge for the patient and the clinician, as well as increasing the overall cost burden to institutions, insurance carriers, and patients.

Oral mucositis is generally associated with radiation therapy to the head and neck and cytotoxic agents such as fluorouracil (5-FU), bleomycin, cytarabine (Cytosar-U, Depocyt, generics), doxorubicin (Doxil, generics), methotrexate (Trexall, generics), and paclitaxel (Abraxane, Taxol, generics).[2,5] The emergence of targeted agents was thought to hold a promise of lowering overall oral mucositis incidence; however, a high incidence of oral mucositis is reported in patients receiving mTOR inhibitors and other targeted agents.[6] The etiology of oral mucositis is different with these new agents compared with oral mucositis caused by radiation and standard cytotoxic agents.[7] Numerous

TABLE 1. Demographics of Rush study population

Cancer type	Number of patients
Tongue/base of tongue	26
B-cell lymphoma	1
Esophageal cancer	7
Hypopharynx	2
Large cell lymphoma	1
Larynx	12
Mandible/retromolar	3
Maxillary sinus	3
Melanoma	2
Metastatic colon	1
Mucoepidermoid carcinoma	1
Nasal cavity	3
Nasopharynx	4
Non-Hodgkin lymphoma	1
Oropharynx	2
Other head and neck	7

Cancer type	Number of patients
Parotid	5
Salivary gland	1
Sinus	1
Soft palate	1
Supraglottic larynx	5
Thyroid	6
Tonsil	25
Trachea	1
Unknown primary	6

Other demographic data	
Average age	59 y
Age range	14-85 y
Percent male	73%
% With chemotherapy	47%
% Nonadherent	20%

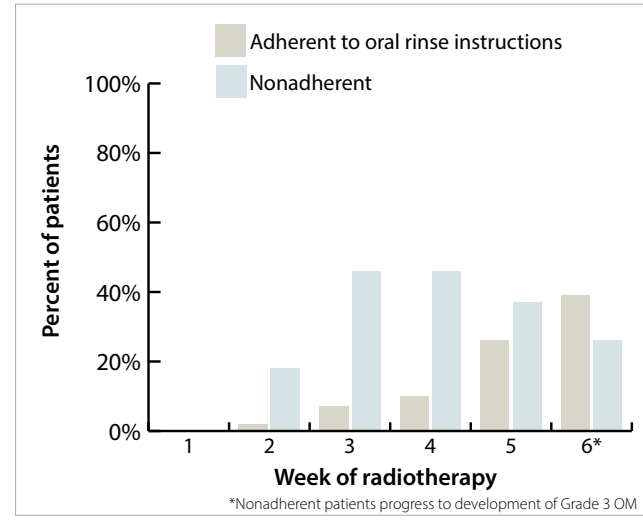

FIGURE 1. Progression to grade 2 mucositis, week 1 to week 6

pharmacologic approaches for prevention and treatment have been investigated; however, given the diversity of mucositis etiology, a single pharmacologic approach is not likely to be successful when a broad spectrum of anticancer treatments could be the cause.

A common feature of oral mucositis from all causes is mucosal damage. One approach to slowing mucositis progression, no matter the etiology, is to provide a protective barrier over the mucosa. Although a number of oral rinses have been tried, they either lack evidence-based supportive data of benefit or are not recommended in the guidelines from the European Society of Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology (ASCO), the American Society of Radiation Oncology (ASTRO), or the Oncology Nursing Society (ONS).[8] These products/solutions are mostly suboptimal treatments; however, many of them continue to be used because not many evidence-based therapeutic options are available. Managing the adverse effects of OM is extremely frustrating for oncology nurses, resulting in a willingness to try anything that could potentially help patients.

At Rush University Medical Center, most of these products were also unsuccessful in alleviating OM in our patients. We decided to try MuGard, a new mucoadhesive polymer oral wound rinse from Access Pharmaceuticals Inc, shortly after it became available in the United States. An initial clinical study by Access Pharmaceuticals on the use of MuGard by patients with head and neck cancer undergoing chemoradiation indicated that the product significantly reduced the severity of oral mucositis, compared with historical controls, when its use began at the same time as cancer therapy. Interim results of a randomized, double-blind, placebo-controlled study, also in head and neck patients undergoing chemoradiation, demonstrated a meaningful treatment benefit, with several parameters reaching statistical significance.[9] In parallel with that study, a clinical evaluation of MuGard for OM was conducted at Rush University Medical Center to investigate its clinical effect on pain severity, need for narcotics during treatment and posttreatment recovery, OM toxicity, and the patients' ability to maintain their weight while undergoing radiation/chemoradiation for cancers in the head and neck region. This article summarizes the results of the Rush University clinical evaluation.

METHODS AND ANALYSIS

We prescribed MuGard to 128 patients who were commencing radiation therapy for a primary head and neck cancer over an 18-month period (**Table 1**). Patients were instructed to gently swish and swallow 5 mL of MuGard four to six times a day starting on the first day of cancer treatment and

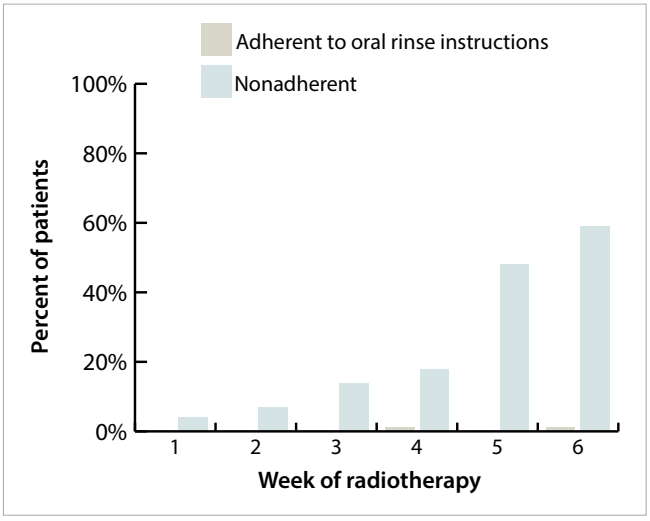

FIGURE 2. Progression to grade 3 mucositis, week 1 to week 6

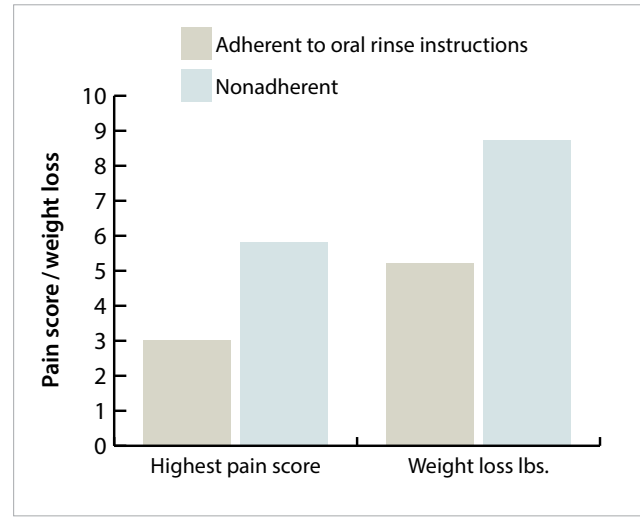

FIGURE 3. Pain scores and weight loss

continuing for 1 week or longer after their last treatment. The patient's weight, pain assessment (on a scale of 0 to 10), oral assessment, and National Cancer Institute (NCI) OM toxicity were documented biweekly. In analyzing the data, we found that 102 of the patients adhered to the patient instructions. Therefore, for the purpose of further analysis, the data were divided into two cohorts: those who adhered to the instructions given for use and those who were nonadherent. Statistical analyses were conducted by grouping the data into 2x2 contingency tables and determining *P* values according to two-sided (two-tailed) Fisher's exact test. An association between the cohorts (adherent and nonadherent) and an outcome parameter was considered to be significant with a *P* value of less than .05.

FINDINGS AND IMPLICATIONS

For the purpose of data analysis, patients who failed to adhere to the instructions for using the oral rinse (ie, they did not use the rinse or used it infrequently) were the control cohort. Eleven patients dropped out of the evaluation before completing at least 6 weeks of treatment. Data from these patients were included in the analysis.

The patients who adhered to the instructions for using the oral rinse had a mean OM grade of 1 to 2 on the NCI OM toxicity grading scale, maintained their weight, and reduced their need for narcotics. Of the 26 patients who did not use the oral rinse as instructed, 13 of them developed grade 3 OM. Our results indicate that MuGard is a powerful tool for reducing OM incidence, significant weight loss, and narcotic use in patients undergoing radiation therapy to the head and neck region. This evaluation correlates with the findings of a randomized, placebo-controlled study in which MuGard was found to be more effective than saline bicarbonate rinse for OM in 70 patients.[9]

RESULTS

Our data demonstrate that progression to grade 2 mucositis was delayed during weeks 1 to 5 in the adherent group (**Figure 1**). Progression to grade 3 mucositis occurred in 50% of patients in the nonadherent cohort by week 5, compared with 1% of the patients who adhered to the oral rinse regimen (**Figure 2**). The combined incidence of grades 2 and 3 mucositis was 91% in the nonadherent cohort, compared with 41% in the adherent cohort.

Patients in the nonadherent group fared worse in all parameters used for comparison between the two cohorts. The mean of the highest reported pain scores (3.0 vs 5.8; $P<.001$; ANOVA single factor) and average weight loss (5.2 lb vs 8.7 lb; $P=.0034$; ANOVA single factor) were higher in the group that did not adhere to the rinse usage instructions (**Figure 3**). Reported levels of pain were higher in the patients in the nonadherent cohort compared with those in the adherent group. In addition, the percentages of patients in the nonadherent group, compared with those of the adherent group, using analgesics (96% vs 70%, respectively; $P=.004$; Fisher's exact test), using gastrostomy tube (G-tube) for nutrition (50% vs 37%, respectively; $P=.2666$; Fisher's exact test), and who developed thrush (65% vs 25%, respectively; $P=.0002$; Fisher's exact test) were greater (see the online version of this article for graphs illustrating the comparison of pain relief and use of analgesics, use of gastrostomy tube, and incidence of thrush). At Rush University, prophylactic

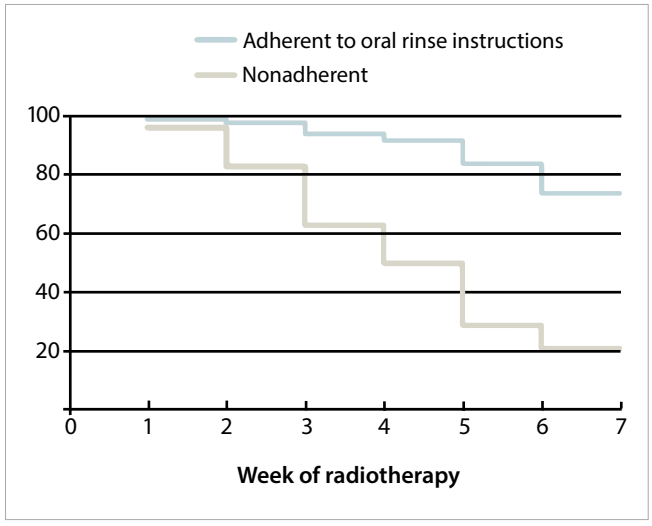

FIGURE 4. Percentage of patients not yet reporting the onset of pain exceeding 4 on a scale of 0 to 10

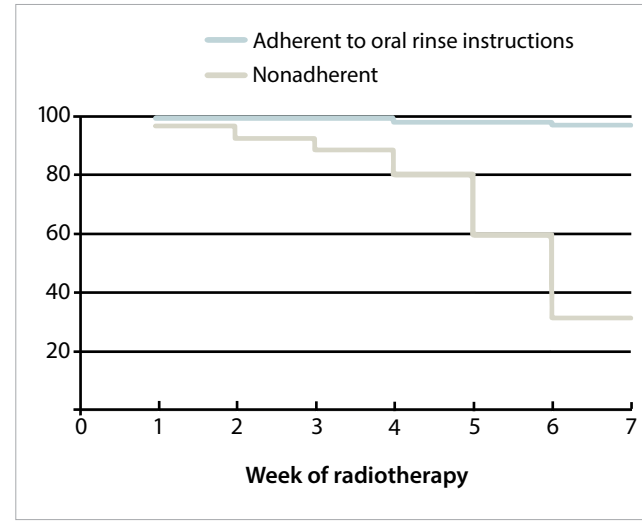

FIGURE 5. Percentage of patients not yet experiencing the onset of oral mucositis grade 2 or higher

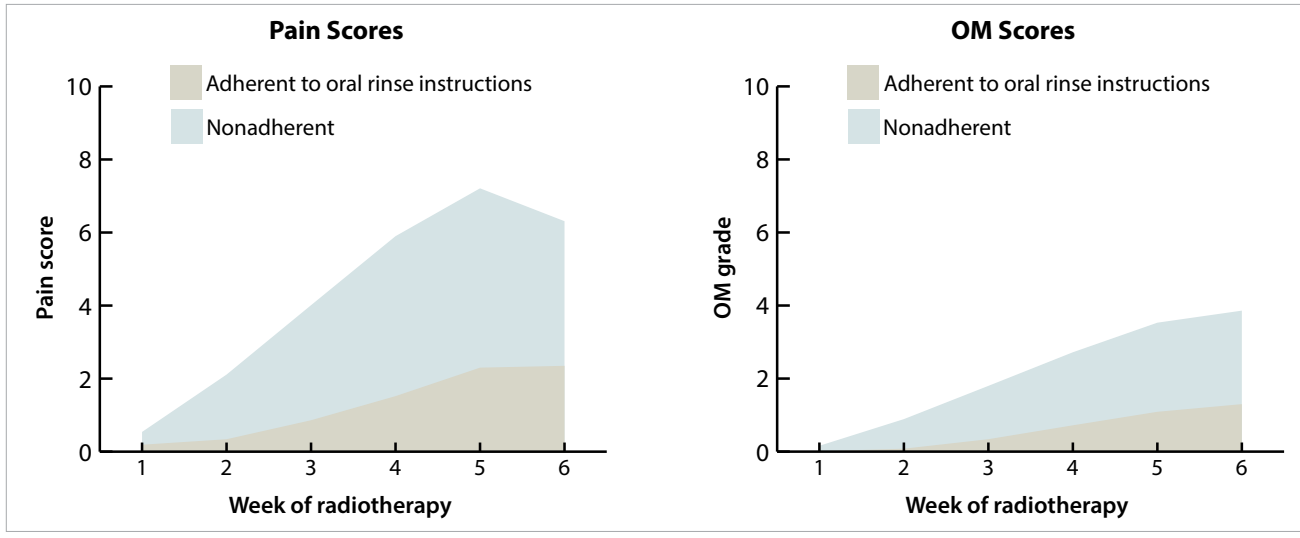

FIGURE 6. Mean weekly pain and oral mucositis scores over 6 weeks of radiotherapy

G-tubes are recommended and placed in all patients with head and neck cancer. The G-tubes are typically used during the course of therapy; however, patients are also encouraged to drink fluids orally throughout treatment to maintain their swallowing ability. Some patients have refused placement of the tubes.

In a further demonstration of the clinical benefit of MuGard, substantial delays were noted in time to onset of both pain and mucositis. Onset of either reported pain scores exceeding 4 or observed OM grade exceeding 2 were analyzed. Displayed as Kaplan Meier (survival) plots, the results demonstrate substantial delays in onset of both pain (**Figure 4**) and mucositis (**Figure 5**) in the adherent cohort compared with the nonadherent group.

STATISTICAL ANALYSES

Additional analyses of the data determined whether the observed benefits of MuGard were statistically significant. In reporting their results from the NCT01283906 trial, Allison and colleagues used several standard methods to analyze the data.[9] One method compared the areas under the curve (AUCs) of patients' daily reported mouth and

throat soreness scores during the course of radiation therapy. A similar method was used to analyze data in this study, reviewing individual AUCs of weekly scores for pain and OM, and conducting an analysis of variance (ANOVA) test of the two sets of AUC values (**Figure 6**). The AUC provides a measure of the total pain experienced by a patient over the entire course of radiation therapy. The plots indicate that the adherent cohort experienced considerably lower levels of pain and OM compared with the nonadherent group. At all time points, the mean pain score in the adherent group was lower than that in the nonadherant group. ANOVA test of the two data sets showed that these results are extremely statistically significant, with *P* values well below .0001.

By counting the numbers of patients in each cohort who used analgesics, developed thrush, or lost more than 6 lb in weight, we were able to use the two-tailed Fisher's exact test to determine that the differences in these parameters for the two cohorts were significant. Analgesia use, development of thrush, and weight loss were statistically lower in the MuGard-adherent group than in the nonadherent group (**Table 2**).

CONCLUSIONS

A clinical evaluation at Rush University Medical Center was able to duplicate the results of clinical studies on the use of the oral rinse MuGard in patients with head and neck cancer who were undergoing radiation therapy. Patients who adhered to the instructions provided for using the oral rinse experienced significant clinical benefits including lower grade of oral mucositis, less pain, reduced analgesic use, and were better able to maintain their weight. Based on the results of this evaluation, the use of MuGard has been adopted into the standard of care at our institution for patients at risk for developing oral mucositis as a result of cancer therapy. ■

TABLE 2. Statistical analysis results of population comparisons using Fisher's exact test

	Used analgesics	Did not use analgesics	Total	
Adherent	71	31	102	The two-tailed *P* value is .0044 (very statistically significant)
Nonadherent	25	1	26	
Total	96	32	128	
	Developed thrush	**Did not develop thrush**	**Total**	
Adherent	28	74	102	The two-tailed *P* value is .0002 (extremely statistically significant)
Nonadherent	18	8	26	
Total	46	82	128	
	Lost <7 pounds	**Lost >6 pounds**	**Total**	
Adherent	74	27	101	The two-tailed *P* value is .0020 (very statistically significant).
Nonadherent	10	16	26	
Total	84	43	127	

Note: Two-tailed P value was determined using QuickCalcs http://graphpad.com/quickcalcs/contingency1.cfm.

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Go to OncologyNurseAdvisor.com/mucositis for additional graphs illustrating results of the study on use of MuGard at Rush University Medical Center.