Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 5, pp. 1460–1466, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.01.031

CLINICAL INVESTIGATION **Breast**

MOMETASONE FUROATE EFFECT ON ACUTE SKIN TOXICITY IN BREAST CANCER PATIENTS RECEIVING RADIOTHERAPY: A PHASE III DOUBLE-BLIND, RANDOMIZED TRIAL FROM THE NORTH CENTRAL CANCER TREATMENT GROUP N06C4

Robert C. Miller, M.D., M.S.,* David J. Schwartz, M.D.,† Jeff A. Sloan, Ph.D.,‡ Patricia C. Griffin, M.D.,§ Richard L. Deming, M.D.,¶ Jon C. Anders, M.D.,‖ Thomas J. Stoffel, M.D.,# Robert E. Haselow, M.D.,** Paul L. Schaefer, M.D.,†† James D. Bearden III, M.D.,§ Pamela J. Atherton, M.S.,‡ Charles L. Loprinzi, M.D.,* and James A. Martenson, M.D.*

*Department of Radiation Oncology, ‡Division of Biomedical Informatics and Biostatistics, Mayo Clinic, Rochester, MN; †Minneapolis Radiation Oncology, P.A., Minneapolis, MN; §Upstate Carolina Community Clinic Oncology Program, Spartanburg, SC; ¶Iowa Oncology Research Association Community Clinic Oncology Program, Des Moines, Iowa; ‖Wichita Community Clinical Oncology Program, Wichita, KS; #Cedar Rapids Oncology Project Community Clinic Oncology Program, Cedar Rapids, IA; ††Toledo Community Hospital Oncology Program Community Clinic Oncology Program, Toledo, OH; **Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, MN

Purpose: A two-arm, double-blind, randomized trial was performed to evaluate the effect of 0.1% mometasone furoate (MMF) on acute skin-related toxicity in patients undergoing breast or chest wall radiotherapy.

Methods and Materials: Patients with ductal carcinoma *in situ* or invasive breast carcinoma who were undergoing external beam radiotherapy to the breast or chest wall were randomly assigned to apply 0.1% MMF or placebo cream daily. The primary study endpoint was the provider-assessed maximal grade of Common Terminology Criteria for Adverse Events, version 3.0, radiation dermatitis. The secondary endpoints included provider-assessed Common Terminology Criteria for Adverse Events Grade 3 or greater radiation dermatitis and adverse event monitoring. The patient-reported outcome measures included the Skindex-16, the Skin Toxicity Assessment Tool, a Symptom Experience Diary, and a quality-of-life self-assessment. An assessment was performed at baseline, weekly during radiotherapy, and for 2 weeks after radiotherapy.

Results: A total of 176 patients were enrolled between September 21, 2007, and December 7, 2007. The provider-assessed primary endpoint showed no difference in the mean maximum grade of radiation dermatitis by treatment arm (1.2 for MMF vs. 1.3 for placebo; $p = .18$). Common Terminology Criteria for Adverse Events toxicity was greater in the placebo group ($p = .04$), primarily from pruritus. For the patient-reported outcome measures, the maximum Skindex-16 score for the MMF group showed less itching ($p = .008$), less irritation ($p = .01$), less symptom persistence or recurrence ($p = .02$), and less annoyance with skin problems ($p = .04$). The group's maximal Skin Toxicity Assessment Tool score showed less burning sensation ($p = .02$) and less itching ($p = .002$).

Conclusion: Patients receiving daily MMF during radiotherapy might experience reduced acute skin toxicity compared with patients receiving placebo. © 2011 Elsevier Inc.

Breast neoplasms, Mometasone furoate, Radiotherapy, Skin manifestations, Toxicity.

INTRODUCTION

Radiation dermatitis is a common adverse effect of radiotherapy in patients undergoing irradiation of the breast and/or chest wall. It is the most common treatment-related toxicity for patients undergoing RT for early-stage breast cancer (1). Although many topical agents are currently used in clinical practice for the prevention and treatment of radiation dermatitis, the results from randomized clinical trials have not consistently indicated the superiority of any single agent. However, a recent randomized clinical trial of mometasone

Reprint requests to: Robert C. Miller, M.D., M.S., Department of Radiation Oncology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: miller.robert@mayo.edu

Conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic and supported by U.S. National Institutes of Health Grant CA 124477 (principal investigator, Charles Loprinzi, M.D.).

Presented as a late-breaking abstract at the 50th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Boston, MA, September 22, 2008.

Conflict of interest: none.

Received Sept 11, 2009, and in revised form Nov 19, 2009. Accepted for publication Jan 2, 2010.

furoate (MMF) combined with an emollient cream vs. an emollient cream alone showed a reduction in dermatitis and patient symptoms in the MMF arm (2–6). The present clinical trial was conducted as a confirmatory trial to assess the value of MMF in decreasing the treatment-related skin toxicity of patients receiving adjuvant therapy for breast cancer.

METHODS AND MATERIALS

The North Central Cancer Treatment Group performed a two-arm, double-blind, randomized trial designed to evaluate the effect of MMF on skin-related toxicity in breast cancer patients undergoing RT to the breast (breast conservation therapy) or chest wall (postmastectomy RT). The Mayo Clinic Institutional Review Board and the institutional review board of the participating institutions independently approved the present study. All patients provided written informed consent before enrollment in the trial. The study registration numbers were NCCTG-N06C4 and NCT00438659.

Patient selection criteria

The patients eligible for enrollment in the present trial were adults (age, ≥18 years) with histologic proof of a primary invasive breast carcinoma or ductal carcinoma *in situ* who were to undergo a planned course of continuous, definitive, or adjuvant external beam RT to the whole breast as part of breast conservation therapy or to the chest wall as a part of postmastectomy RT (minimal prescription dose, 50.0 Gy). Treatment of the regional lymph nodes, including the axillary, supraclavicular, and internal mammary lymph nodes, was permitted. The daily treatment dose was 1.75–2.12 Gy. Patients could enter the trial before receiving the third radiation fraction. An Eastern Cooperative Oncology Group performance status of 0, 1, or 2 was required.

The ineligibility criteria included the presence of inflammatory carcinoma of the breast or a known allergy or hypersensitivity to mometasone and furoate, imidazolidinyl urea, or formaldehyde. Additional ineligibility criteria included the use of leukotriene inhibitors or the use of a prescription or over-the-counter medication that contained hydrocortisone or any other cortisone- or corticosteroid-containing preparation. Patients were not eligible for the present trial if they had pre-existing loss of skin integrity or previous RT to the area being treated. Also excluded were women who were pregnant or breastfeeding and women of child-bearing age who were unwilling to use adequate contraception during the study period. Patients with bilateral breast carcinoma were ineligible, as were patients receiving partial (<75%) breast treatment.

Randomization

The patients were randomly assigned, in a double-blind manner using a dynamic allocation procedure, to either 0.1% MMF cream or an identical-appearing placebo cream (Dermabase, Paddock Laboratories, Minneapolis, MN). Randomization was performed through the operations office of the North Central Cancer Treatment Group (Rochester, MN). The stratification factors included whole-breast RT after lumpectomy vs. chest wall RT after mastectomy, treatment vs. no treatment of regional lymph nodes, and total radiation dose of 50.0–55.0 Gy vs. >55.0 Gy.

Treatment

Patients were instructed to apply 3 mL of MMF cream or placebo cream lightly once daily to the area under treatment at not less than 4 hours before or after RT until completion of the prescribed RT course. They were instructed to vary the amount of cream on the basis of body habitus and to cover the entire treated area. No other topical agents were allowed to be used in the RT field while the patient was receiving the study medication. If, in the judgment of a patient's clinician, radiation dermatitis necessitated initiation of an agent other than the study medicine, the patient was to discontinue the study medication and continue with the evaluations in accordance with the study protocol.

Study evaluation

The patients were evaluated at baseline and at weekly intervals during their RT by their treatment providers (Table 1). The evaluation consisted of a provider-assessed toxicity assessment using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (7), and patient-reported symptoms and quality of life (QOL) noted in the patient-completed assessment forms. Additionally, after RT completion, the patients completed a patient questionnaire booklet for the 2 weeks immediately after RT completion. The patient-reported outcomes were measured using the Skindex-16, the CTCAE Symptom Experience Diary, and the Skin Toxicity Assessment Tool.

The Skindex-16 is an analog scale of symptoms and functional endpoints related to skin toxicity that can occur in the treatment area (8). The Symptom Experience Diary requires the patient to rate the severity of multiple skin toxicity-related signs and symptoms on a scale of 0 (do not experience) to 10 (experience all the time). The Skin Toxicity Assessment Tool is a skin-specific instrument consisting of a provider-assessed objective measure of skin changes and five measures of patient-reported discomfort (9). The patient-completed QOL assessment was the linear analog self-assessment. It consisted of six questions, with responses ranging from 0 (poor QOL) to 10 (best QOL). These questions have been validated as general measures of global QOL dimensional constructs in numerous settings and have been validated at Mayo Clinic for use in cancer patients (10–13).

Statistical analysis

The primary study endpoint was radiation dermatitis determined by the patient's health care provider with CTCAE version 3.0. The maximal grade of this adverse event during treatment was evaluated for each patient. The mean maximal grades were compared between the two treatment arms with a single two-sample t test. We calculated that a two-sample t test (two-sided $\alpha = 0.05$) with 64 patients in the MMF group and 64 patients in the placebo group would have an 80% power to detect a difference of one-half standard deviation (approximately 0.4 of a severity grade according to the standard deviation of the placebo arm in the double-blind portion of North Central Cancer Treatment Group 909252, ''Phase III Double-Blind Evaluation of an Aloe Vera Gel as a Prophylactic Agent for Radiation-Induced Skin Toxicity'') (6). The sample size was increased by 15% to account for missing data (*e.g.,* patient ineligibility, cancellation of trial participation). The total number planned for accrual was 148 patients, or 74 per treatment arm.

The secondary endpoints included the incidence of severe (CTCAE grade 3 or greater) radiation dermatitis, grade of adverse events at the end of RT, and the maximal grade of other adverse events, the latter 2 endpoints were measured using the CTCAE version 3.0. These endpoints were compared between the treatment and placebo arms using the chi-square test and Fisher's exact test, as appropriate. The secondary endpoints of patient-reported skin toxicity (Skindex-16 and Skin Toxicity Assessment Tool) and QOL were

Table 1. Evaluation schedule of Phase III trial

Tests and procedures	Baseline	Weekly during RT*	Observation and follow-up†
Provider-assessed toxicity			
CTCAE dermatitis assessment	Yes	Yes	NA
Adverse-event assessment (CTCAE version 3.0)	Yes	Yes	NA
Provider-assessed and patient-reported toxicity			
Skin toxicity assessment	Yes	Yes	NA
Patient-reported toxicity			
LASA, Skindex-16, and Symptom Experience Diary	Yes	Yes	Yes

Abbreviations: RT = radiotherapy; CTCAE = common terminology criteria for adverse events; LASA = linear analog self-assessment; NA = not applicable.

* At clinic visit.

† Follow-up period was 2 weeks after RT completion.

analyzed by comparing the mean responses between the study arms using the Kruskal-Wallis test.

RESULTS

A total of 176 patients were enrolled between September 21, 2007, and December 7, 2007 (Fig. 1). The follow-up period was the 2 weeks after RT completion. This enrollment exceeded the original target accrual by 28 patients and resulted from an extremely rapid rate of enrollment. Of the 176 patients, 90 were randomly assigned to the treatment group and 86 patients were randomly assigned to the control group. After randomization, 5 patients in the MMF arm and 2 patients in the placebo arm declined participation, for 169 eligible patients. Data were missing for 3 patients, leaving 166 patients eligible for evaluation of the primary endpoint. The baseline characteristics were equally balanced between the study agent arm and the placebo arm (Table 2).

No significant difference was found in the mean maximal grade of provider-assessed radiation dermatitis (1.2 in the MMF arm vs. 1.3 in the placebo arm; p =.18; Table 3). Similarly, no significant difference was found in the incidence of provider-assessed severe (CTCAE grade 3 or greater) radiation dermatitis or the provider-assessed maximal radiation dermatitis grade.

A number of secondary endpoints were positive for a reduction in skin toxicity in the MMF group. Itching, irritation, the persistence of symptoms, the recurrence of toxicity symptoms, and annoyance with dermatitis were all reduced by a statistically significant fraction in the treatment group compared with the placebo group in the Skindex-16 (Table 4). The total Skindex-16 score was 1.4 in the MMF arm and 1.7 in the placebo arm (p = .07), suggesting a trend toward a more favorable outcome for the patients treated with MMF. The patients in the MMF arm also reported less discomfort and burning (p = .02), less itching (p = .002), and less redness (p = .003; Table 5) using the Skin Toxicity Assessment Tool and Symptom Experience Diary. Significantly less itching was observed in the patients in the MMF arm after approximately Week 2 (Fig. 2). No difference was found in overall QOL using the linear analog self-assessment instrument. The MMF group had a mean score of 8.3 (median, 9.0), and the placebo group had a mean score of 8.4 (median, 9.0). Similarly, no difference was found in the six linear analog self-assessment subdomains.

The adverse event monitoring by providers using CTCAE, version 3.0, showed a greater mean maximal grade of any type of toxicity in the placebo group than in the treatment group (p = .04; Table 6). This difference was largely secondary to the maximal grade of pruritus being greater in the placebo group (p = .005), with 6% of patients reporting Grade 3 pruritus vs. 1% in the MMF group, and 61% of patients reporting mild pruritus in the placebo group vs. 36% in the MMF group.

DISCUSSION

Radiation dermatitis is a common adverse effect in patients undergoing RT to the breast and chest wall. Clinically, the severity of this symptom is related to its dose and fractionation delivered to the skin and to patient-related factors such as obesity, smoking, and use of radiosensitizing chemotherapy (4, 14).

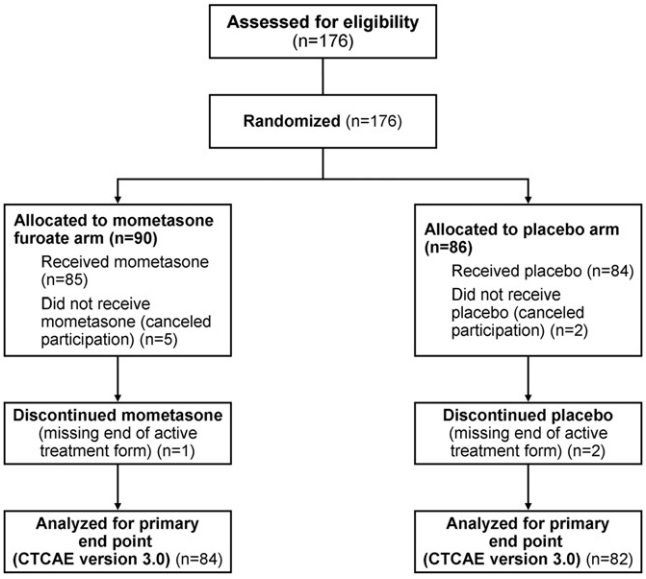

Fig. 1. Flow of patients in Phase III trial. CTCAE = Common Terminology Criteria for Adverse Events.

Table 2. Baseline characteristics

Characteristic	Group			*p*
	MMF (*n* = 85)	Placebo (*n* = 84)	Total (*n* = 169)	
Age (y)				.38
Median	60	57	58	
Range	35–89	27–85	27–89	
Radiation fields				.81
Breast (after lumpectomy)	71 (84)	69 (82)	140 (83)	
Chest wall (after mastectomy)	14 (16)	15 (18)	29 (17)	
Regional lymph nodes				.44
Treated	18 (21)	22 (26)	40 (24)	
Not treated	67 (79)	62 (74)	129 (76)	
Planned total radiation dose (Gy)				.33
50.0–55.0	17 (20)	12 (14)	29 (17)	
>55.0	68 (80)	72 (86)	140 (83)	

Abbreviation: MMF = mometasone furoate.

Data are presented as number of patients, with percentages in parentheses, unless otherwise noted.

Acute radiation dermatitis is associated with an inflammatory cascade thought to be cytokine mediated, although its exact mechanisms are unclear. *In vitro* studies of irradiated human skin have shown alterations to the normal histologic characteristics, including a marked decrease in basal cell proliferation, endothelial cell damage, and resultant vasodilation with altered membrane permeability, and inflammatory cytokine release (1, 15, 16). Corticosteroids act as anti-inflammatory agents by regulating leukocyte adhesion to endothelial cells, inducing vasoconstriction, decreasing capillary permeability, and inhibiting leukocyte proliferation and migration. They have been shown to decrease the expression of interleukin-6 *in vitro* (17).

No clear consensus about the superiority of any single topical agent in the prevention and treatment of radiation dermatitis has emerged, despite decades of investigations (3, 6, 18–22). Corticosteroid preparations have been investigated as agents for the treatment of radiation dermatitis since shortly after synthetic corticosteroids were first used clinically (23).

Scott and Kalz (24) found that a single application of various corticosteroid preparations was capable of either ameliorating or delaying the onset of radiation dermatitis in a small cohort of patients undergoing RT with grenz rays. Bjornberg *et al.* (25) performed a double-blind comparison of fluocinolone acetonide vs. placebo in 26 patients and demonstrated a statistically significant decrease in the degree of overall dermatitis at 3 weeks after therapy initiation; however, the difference was no longer significant at 6 weeks. Bjornberg *et al.* (26) also conducted a double-blind comparison of bethamethasone-17-valerate vs. Vaseline (Unilever United States, Englewood Cliffs, NJ) and vs. Eucerine (Beiersdorf AG, Hamburg, Germany) in 26 patients. A statistically significant difference was found in favor of bethamethasone compared with Vaseline or Eucerine. This difference was no longer significant at 6 weeks, however. Repeat checks of the skin at 2 to 4 months showed no statistically significant difference among the 3 groups in atrophic skin lesions in the treatment area (26). Later trials exploring the use of corticosteroids did not find a statistically significant difference between patients treated with corticosteroid preparations and those treated with other agents or placebo (27–29).

More recently, two double-blind, randomized trials have evaluated the use of corticosteroids in preventing radiation dermatitis. The first of these trials evaluated MMF cream plus emollient cream compared with a placebo emollient cream (2). Those patients receiving MMF and emollient cream experienced less radiation dermatitis than the placebo group ($p = .003$). Also, an indication was found for less burning sensation ($p = .069$) and less pain ($p = .087$) in the MMF-treated patients. The second trial evaluated the topical preparations 0.1% methylprednisolone vs. 0.5% dexpanthenol in a cohort of patients undergoing RT for breast cancer (30). The investigators reported that, although neither agent

Table 3. Provider-assessed primary and secondary endpoints with use of CTCAE, version 3.0

Endpoint	Group			*p*
	MMF (*n* = 84)	Placebo (*n* = 82)	Total (*n* = 166)	
Provider-assessed primary endpoint				
Maximal radiation dermatitis grade				
Mean ± standard deviation	1.2 ± 0.85	1.3 ± 0.80	1.3 ± 0.83	.18
Range	0.0–3.0	0.0–3.0	0.0–3.0	
Provider-assessed secondary endpoints				
Incidence of severe (grade 3 or greater) radiation dermatitis				
No	80 (95)	78 (95)	158 (95)	.97
Yes	4 (5)	4 (5)	8 (5)	
Maximal radiation dermatitis grade				
0	20 (24)	13 (16)	33 (20)	.51
1	34 (40)	32 (39)	66 (40)	
2	26 (31)	33 (40)	59 (36)	
3	4 (5)	4 (5)	8 (5)	

Data are presented as numbers of patients, with percentages in parentheses, unless otherwise noted.

Table 4. Patient-reported maximum Skindex-16 toxicity score*

Toxicity characteristic	Maximum Skindex-16 score: MMF (n = 83)	Placebo (n = 84)	Change in score	p
Itching	2.3	3.1	−0.8	.008
Burning or stinging	2.6	3.1	−0.5	.06
Pain	2.5	2.9	−0.4	.15
Irritation	2.6	3.4	−0.8	.01
Persistence or recurrence	2.3	3.0	−0.7	.02
Worry about skin condition	1.5	1.8	−0.3	.45
Appearance	1.6	2.0	−0.4	.10
Frustration	1.5	1.8	−0.3	.23
Embarrassment	0.7	1.2	−0.5	.07
Annoyance	1.2	1.8	−0.6	.04
Depression	0.8	1.1	−0.3	.24
Interaction with others	0.8	1.0	−0.2	.30
Desire to be with people	0.7	0.8	−0.1	.43
Shows affection	0.8	1.0	−0.2	.79
Effect on daily activities	1.2	1.4	−0.2	.24
Work or do what enjoy	1.2	1.4	−0.2	.43
Total Skindex-16 score	1.4	1.7	−0.2	.07

Abbreviation: MMF = mometasone furoate.
* Lower score indicated less toxicity.

reduced the incidence of radiation dermatitis, both agents delayed the onset of the maximal clinical symptoms by 1 week compared with the control cohort.

An analysis of the primary study endpoint in the present trial, the maximal grade of provider-assessed radiation dermatitis using CTCAE version 3.0, showed no significant difference in the dermatitis grades. Most patients had only grade 1 or 2 toxicity, and the narrow range of toxicity limited our ability to assess MMF's effect on radiation dermatitis. However, secondary patient-reported measures of toxicity, including the Skindex-16, Skin Toxicity Assessment Tool, and Symptom Experience Diary, did suggest a modest benefit in patients treated with MMF. Moreover, overall toxicity, evaluated with CTCAE version 3.0, was decreased in the MMF-treated patients, primarily because of decreased pruritus in the MMF group. Overall, patient QOL did not appear to be affected by use of the study agent and the reduction in toxicity reported for skin symptoms.

These findings are consistent with those of Bostrom *et al.* (2), whose results suggested a modest reduction in radiation dermatitis in the MMF-treated patients during breast RT. Our

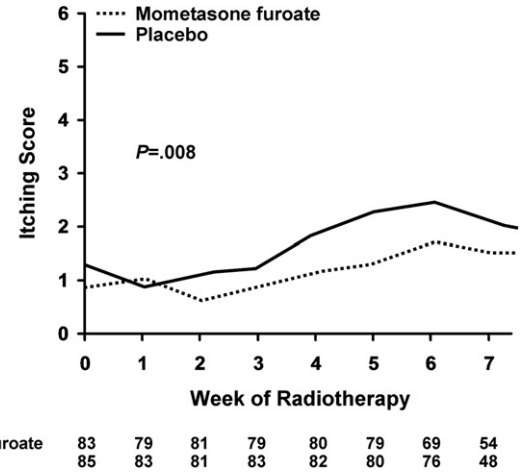

Fig. 2. Mean itching score by week of radiotherapy. Score measured using Skindex-16 instrument. Maximal mean Skindex-16 score was 2.3 for mometasone furoate group and 3.1 for placebo group.

Table 5. Maximal patient-reported Skin Toxicity Assessment Tool and Symptom Experience Diary toxicity scores*

Characteristic	Maximal score: MMF (n = 83)	Placebo (n = 84)	p
Skin Toxicity Assessment Tool			
Discomfort or burning	1.5	2.1	.02
Itching	1.5	2.2	.002
Pulling	1.0	1.4	.07
Discomfort or tenderness	2.1	2.5	.11
Symptom Experience Diary			
Redness	5.1	6.8	.003
Dry peeling	2.7	3.4	.52
Wet peeling	1.3	1.6	.97
Weeping	1.2	1.4	.65
Rash	2.6	4.0	.01
Swelling	2.3	2.4	.70
Fatigue	4.5	5.0	.24
Decrease in color	2.3	2.1	.72
Band, stripes, or lines	1.7	1.5	.72

Abbreviation: MMF = mometasone furoate.
* Lower score indicated less toxicity.

Table 6. Provider-assessed maximal CTCAE version 3.0 toxicity grade

Toxicity type and grade*	Group: MMF (n = 84)	Placebo (n = 82)	$p^\dagger$
Pruritus			.005
0	33 (39)	13 (16)	
1	36 (43)	50 (61)	
2	14 (17)	14 (17)	
3	1 (1)	5 (6)	
4	0	0	
Worst grade of any type of toxicity			.04
0	23 (27)	5 (6)	
1	34 (40)	50 (61)	
2	25 (30)	20 (24)	
3	2 (2)	7 (9)	
4	0	0	

Abbreviations: CTCAE = common terminology criteria for adverse events; MMF = mometasone furoate.
*Grades 0, none; 1, mild; 2, moderate; 3, severe; and 4, life-threatening.
† Wilcoxon rank sum test.

results are also consistent with those from Schmuth *et al.* (30), who found that 0.1% methylprednisolone decreased patient symptoms, despite the lack of a statistically significant reduction in the incidence of radiation dermatitis in our study. The present study was not designed to identify which patients might benefit most from MMF, as determined by known risk factors such as obesity, smoking history, daily radiation fraction size, and history of chemotherapy (4, 14). Patients were not stratified by fraction size, although a statistically significant difference was not present between treatment groups according to the total RT dose. Another unknown factor is whether MMF is effective when its use is delayed until the onset of patient-reported symptoms, typically around the third week of therapy. This factor will be addressed in a future North Central Cancer Treatment Group trial.

The patient-reported outcomes have been defined by the U.S. Food and Drug Administration as a measure of the patient's health status that is obtained from the patient without interpretation by the physician. In recent years, interest has grown in using reports obtained directly from patients without intervening interpretation by their care providers. The patient-reported outcome measures in the present study delineated a wider spectrum of toxicity than the provider-assessed measures using the CTCAE version 3.0. Although the primary study endpoint did not show a positive effect with MMF on reducing radiation dermatitis, the secondary measures suggested a value to the prophylactic use of MMF in reducing skin toxicity during breast RT (31, 32).

CONCLUSION

No reduction in radiation dermatitis during RT for breast cancer was observed by the medical providers with the use of MMF, as assessed by the primary study endpoint, and the maximum grade of radiation dermatitis, as assessed using CTCAE version 3.0. However, MMF use reduced the skin toxicity symptoms compared with placebo in terms of pruritus, burning, redness, and other measures, as assessed by the secondary measures in the present study.

REFERENCES

1. Hopewell JW. The skin: Its structure and response to ionizing radiation. *Int J Radiat Biol* 1990;57:751–773.
2. Bostrom A, Lindman H, Swartling C, *et al*. Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: Results from a double-blind, randomized study. *Radiother Oncol* 2001;59:257–265.
3. Fisher J, Scott C, Stevens R, *et al*. Randomized phase III study comparing best supportive care to biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys* 2000;48:1307–1310.
4. Wells M, Macmillan M, Raab G, *et al*. Does aqueous or sucralfate cream affect the severity of erythematous radiation skin reactions? A randomised controlled trial. *Radiother Oncol* 2004; 73:153–162.
5. Wickline MM. Prevention and treatment of acute radiation dermatitis: A literature review. *Oncol Nurs Forum* 2004;31:237–247.
6. Williams MS, Burk M, Loprinzi CL, *et al*. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys* 1996;36:345–349.
7. Cancer Therapy Evaluation Program [Internet]. Rockville, MD: National Cancer Institute [cited 2009 Feb 4]. Common Terminology Criteria for Adverse Events v3.0 (CTCAE); 2006 Aug 9 [cited 2009 Feb 4]. Available from: www.ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed November 20, 2008.
8. Chren MM, Lasek RJ, Sahay AP, *et al*. Measurement properties of Skindex-16: A brief quality-of-life measure for patients with skin diseases. *J Cutan Med Surg* 2001;5:105–110.
9. Berthelet E, Truong PT, Musso K, *et al*. Preliminary reliability and validity testing of a new Skin Toxicity Assessment Tool (STAT) in breast cancer patients undergoing radiotherapy. *Am J Clin Oncol* 2004;27:626–631.
10. Bretscher M, Rummans T, Sloan J, *et al*. Quality of life in hospice patients: A pilot study. *Psychosomatics* 1999;40:309–313.
11. Grunberg SM, Groshen S, Steingass S, *et al*. Comparison of conditional quality of life terminology and visual analogue scale measurements. *Qual Life Res* 1996;5:65–72.
12. Gudex C, Dolan P, Kind P, *et al*. Health state valuations from the general public using the visual analogue scale. *Qual Life Res* 1996;5:521–531.
13. Hyland ME, Sodergren SC. Development of a new type of global quality of life scale, and comparison of performance and preference for 12 global scales. *Qual Life Res* 1996;5: 469–480.
14. Freedman GM, Anderson PR, Li J, *et al*. Intensity modulated radiation therapy (IMRT) decreases acute skin toxicity for women receiving radiation for breast cancer. *Am J Clin Oncol* 2006;29: 66–70.
15. Archambeau JO, Pezner R, Wasserman T. Pathophysiology of irradiated skin and breast. *Int J Radiat Oncol Biol Phys* 1995; 31:1171–1185.
16. Boisnic S, Branchet-Gumila MC, Nizri D, *et al*. Histochemical and biochemical modifications induced by experimental irradiation of human skin maintained in survival conditions and modulation by application of an emulsion containing trolamine. *Int J Tissue React* 2003;25:9–18.
17. Cronstein BN, Kimmel SC, Levin RI, *et al*. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proc Natl Acad Sci USA* 1992;89:9991–9995.
18. Halperin EC, Gaspar L, George S, *et al*., for the CNS Cancer Consortium. A double-blind, randomized, prospective trial to evaluate topical vitamin C solution for the prevention of radiation dermatitis. *Int J Radiat Oncol Biol Phys* 1993;26: 413–416.
19. Heggie S, Bryant GP, Tripcony L, *et al*. A phase III study on the efficacy of topical aloe vera gel on irradiated breast tissue. *Cancer Nurs* 2002;25:442–451.
20. Liguori V, Guillemin C, Pesce GF, *et al*. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. *Radiother Oncol* 1997;42: 155–161.
21. Lokkevik E, Skovlund E, Reitan JB, *et al*. Skin treatment with bepanthen cream versus no cream during radiotherapy: A randomized controlled trial. *Acta Oncol* 1996;35:1021–1026.

22. Vuong T, Franco E, Lehnert S, *et al*. Silver leaf nylon dressing to prevent radiation dermatitis in patients undergoing chemotherapy and external beam radiotherapy to the perineum. *Int J Radiat Oncol Biol Phys* 2004;59:809–814.
23. Marshall AH. The action cortisone on experimental acute roentgen dermatitis. *Acta Radiol* 1953;39:73–77.
24. Scott A, Kalz F. The effect of the topical application of corticotrophin, hydrocortisone, and fluorocortisone on the process of cutaneous inflammation. *J Invest Dermatol* 1956;26: 361–378.
25. Bjornberg A, Hellgren L, Olsson S. Treatment of radiation dermatitis with fluocinolone acetonide. *Acta Radiol Ther Phys Biol* 1965;3:129–134.
26. Bjornberg A, Hellgren L, Magnusson B, *et al*. Topical treatment of radiation dermatitis with bethamethasone-17-valerate, Vaseline and Eucerine: A double-blind comparison. *Clin Radiol* 1967;18:463–464.
27. Glees JP, Mameghan-Zadeh H, Sparkes CG. Effectiveness of topical steroids in the control of radiation dermatitis: A randomised trial using 1% hydrocortisone cream and 0.05% clobetasone butyrate (Eumovate). *Clin Radiol* 1979;30:397–403.
28. Huter KA, Muller HG. [Radiation reaction of the skin in the use of glucocorticoids (German).]. *Strahlentherapie* 1959;108: 475–477.
29. Potera ME, Lookingbill DP, Stryker JA. Prophylaxis of radiation dermatitis with a topical cortisone cream. *Radiology* 1982;143:775–777.
30. Schmuth M, Wimmer MA, Hofer S, *et al*. Topical corticosteroid therapy for acute radiation dermatitis: A prospective, randomized, double-blind study. *Br J Dermatol* 2002;146:983–991.
31. Sloan JA, Berk L, Roscoe J, *et al*., for the National Cancer Institute. Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. *J Clin Oncol* 2007;25:5070–5077.
32. Trotti A, Colevas AD, Setser A, *et al*. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol* 2007;25:5121–5127.