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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

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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