Mometasone Furoate 0.1% versus Eucerin on Moderate to Severe Skin Toxicities in Breast Cancer Patients Receiving Postmastectomy Radiation: A Randomized, Phase III, double-blind Trial

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a double-blinded, randomized trial. Its purpose is to compare the steroid cream mometasone furoate 0.1% (MF), with standard emollient skin care, Eucerin, on the prevention of grade 2 or higher skin toxicities in breast cancer patients receiving PMRT to the chest wall and regional lymph nodes. Patients will be stratified based on two variables: the presence of a reconstruction in order to achieve a balanced population of patients being treated with either photon or electron beams, and body mass index (BMI <30 vs ≥30).

Female breast cancer patients who have received mastectomy + axillary surgery and will undergo postmastectomy radiation (PMRT) at our institution are eligible for this study. Enrollment of 143 patients is expected to take place over 3 years.

Skin toxicities using the Common Terminology Criteria for Adverse Events (CTCAE) v.4 scale will be scored by evaluating RN or MD . Assessments will be completed at baseline, weekly during radiation therapy (RT), and 10-14 days following the completion of RT. Patient-reported skin symptoms will also be assessed at baseline, at week 5 of RT, and 10-14 days following completion of RT.

Screening	Randomization	Pre-RT	Weekly During RT (5 weeks, 50 Gy)	Follow-up (10-14 Days Post-RT)
143 breast cancer patients status post mastectomy + axillary surgery, ± chemotherapy • Stratifications: –Reconstruction Yes vs no –Body Mass Index <30 vs ≥30	Eucerin BID or mometasone furoate 0.1% BID	• Baseline H and P • Baseline Provider Skin Toxicity Assessment • Baseline Skindex-16 questionnaire • Patient education on topical cream usage	• Weekly status checks • Weekly skin cream compliance assessed • Weekly Provider Skin Toxicity • Skindex Questionnaire during Week 5 of RT	• Skin cream compliance assessed • Provider Skin Toxicity Assessment • Skindex-16 questionnaire

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

- To determine if MF, as compared to Eucerin, is effective in preventing grade 2 or higher radiation dermatitis, particularly moist desquamation and/or moderate to brisk erythema in women receiving PMRT

Secondary Objectives

- To compare patient-reported skin symptoms between interventions
- To determine maximum reported skin toxicity and the time to occurrence

3.0 BACKGROUND AND RATIONALE

3.1 Benefit of Postmastectomy Radiation

PMRT is an essential component of treatment for locally advanced breast cancer. The publication of the Oxford Overview meta-analyses of randomized clinical trials in 2005 showed that, compared with surgery alone, the addition of PMRT after mastectomy both reduced the rate of local cancer recurrence and improved 15-year breast cancer mortality by 5% (Clarke, Collins et al. 2005). Although the clinical benefits of PMRT are well established, there is a paucity of data available on the acute toxicities of PMRT, namely, skin toxicities. The majority of studies that examine quality of life after mastectomy focus primarily on cosmetic and psychosocial issues.

3.2 Radiation-Induced Dermatitis

A variety of patient and treatment-related factors such as fractionation schedules, dose, size of the treatment field, concurrent chemotherapy, use of bolus or other beam-modifying devices, and individual genetic variation can affect the intensity of the skin reaction to radiation (Tucker, Turesson et al. 1992). The majority of data available regarding side effects are generated from patients receiving radiation to the intact breast, not the chest wall after mastectomy. Side effects are generally categorized as acute if occurring during or within 6 weeks of radiation treatment and late if occurring >6 weeks after completion of treatment. A common acute toxicity is dermatitis within the irradiated volume. Typically, the skin becomes erythematous and/or hyperpigmented, and may desquamate, in particular in the area of skin folds such as the axilla, supraclavicular fossa, or inframammary fold. Desquamation may be dry or moist. Progressive erythema may be seen after 10-20 Gy, depending on the fractionation schedule (Turesson and Notter 1975), and reaches maximal intensity approximately 1-2 weeks following the completion of treatment. An example of the development of moist desquamation and grade 2 erythema in a woman 1 week post-completion of PMRT to an unreconstructed chest wall is illustrated in Appendix 3.

Factors contributing to variation in the severity of dermatitis in patients receiving PMRT have not been well studied. Acute skin toxicities are generally more severe in the setting of PMRT than breast conservation therapy (BCT), as the skin itself is considered part of the radiation target with PMRT. There are remarkably little data available on the incidence of radiation dermatitis in the post-mastectomy chest wall setting. The three large randomized trials investigating the use of PMRT either do not report toxicity or report late toxicity excluding skin toxicities (Overgaard, Hansen et al. 1997; Overgaard, Jensen et al. 1999; Ragaz, Olivotto et al. 2005). One small retrospective series of 89 patients receiving PMRT using an electron technique reported that 19 patients developed dry desquamation, and only five developed moist desquamation (Hehr, Budach et al. 1999). In contrast, a series of 118 patients treated with a similar technique reported that 52% of patients developed grade 3-4 skin toxicity by Radiation Therapy Oncology Group (RTOG) criteria, and 31% of patients required an unplanned treatment break to recover from early radiation-induced skin toxicities (Spierer, Hong et al. 2004).

The development of normal tissue toxicities in breast cancer patients receiving adjuvant external beam RT demonstrates significant heterogeneity among individuals (Twardella, Popanda et al. 2003), which can be attributed to a variety of individual, tumor stage, cellular, and molecular factors. Increasing evidence suggests that individual genetic variations may also play a significant role in the development of adverse radiation responses (De Ruyck, Van Eijkeren et al.

2005; Andreassen, Alsner et al. 2006; Alsbeih, El-Sebaie et al. 2007), but these remain poorly understood. Existing estimates on rates of radiation dermatitis are extrapolated from patients with intact breasts, who have been treated with a variety of techniques that affect the development of dermatitis. A randomized trial investigating the use of intensity-modulated RT (IMRT) in the setting of BCT demonstrated moist desquamation in 31.2% receiving IMRT and 47.8% with standard treatment, respectively (Pignol, Olivotto et al. 2008). The primary factor that predisposed to moist desquamation was large breast size; race-ethnicity and genetic factors were not assessed in this Canadian study. In Table 1, we summarize the results from the few studies that have specifically evaluated skin toxicities in breast cancer patients who have received PMRT.

Table 1. Incidence of RT-Related Adverse Reactions in PMRT Patients

Sample Size	Skin Toxicities	Study Variables	References
41 PMRT patients	Late tissue fibrosis and telangiectasias	XRCC1&3, TGFB1, SOD2, APEX SNPs	Andreassen et al., 2003
118 PMRT patients	52% grade 3-4 acute skin toxicity	-	Spierer et al., 2004
89 PMRT patients	19 dry desquamation; 5 moist desquamation	-	Hehr et al., 1999

3.3 Evidence for Topical Agents' Prevention and Treatment of Radiation-Induced Dermatitis

Acute radiation dermatitis has been attributed to the combined result of a decrease in functional stem cells, changes in the skin's endothelial cells, inflammation, cell necrosis, and death (Hymes et al. 2006). Proposed mechanisms for the anti-inflammatory effect of corticosteroids include vasoconstriction, decreased capillary permeability, and inhibition of leukocyte proliferation and migration (Yohn,1990). However, all mechanisms are not fully elucidated.

At the present time, there are no established standards for either the prevention or management of radiation-induced skin reactions. Intervention is primarily based on clinician experience. Numerous products are used by various radiation oncology departments throughout the world. Biafene cream (Ortho-McNeil Pharmaceuticals, Titusville, NJ, USA) was evaluated in a multicenter randomized trial conducted by the RTOG and was not found to be superior to standard regimens in the prevention of radiation-induced skin reactions (Fisher, Scott et al. 2000). Generally, it is agreed that a key element of the prevention of radiation dermatitis is moisturizing the irradiated area with Eucerin, Aquaphor, aloe vera, or other hydrophilic products (Maddocks-Jennings, Wilkinson et al. 2005). The emphasis has been on teaching self care to minimize skin trauma, irritation, and or/infection. In our department, we recommend the application of Eucerin BID to the breast or chest wall as standard care for our breast cancer patients. Moist desquamation is treated with Silvadene cream or hydrocolloid dressings.

To date, five trials have evaluated topical corticosteroids for the prevention of acute skin reactions in patients receiving radiation (Bostrom, Lindman et al. 2001; Schmuth, Wimmer et al. 2002; Shukla, Gairola et al. 2006; Omidvari, Saboori et al. 2007; Miller, Schwartz et al. 2011).

The details and results of these studies are summarized in Table 2; however, these studies collectively demonstrated that topical corticosteroid agents used as the sole skin care regimen during irradiation reduced the severity of skin reactions following RT.

Table 2. Select Trials of Topical Steroidal Creams in Breast Cancer Patients Receiving Radiation Therapy

Study (Year)	Study Population, Targeted	Corticosteroid Agent	Outcomes
Bostrom et al, 2001	N=49, whole breast	Mometasone furoate 0.1% vs Placebo	MMF group with significantly decreased acute radiation dermatitis (P=0.0033).
Schmuth et al, 2002	N=36 ,whole breast	0.1%methylprednisolone cream vs 0.5% dexpanthenol cream vs no intervention	No significant difference in mean severity scores of radiation dermatitis
Shukla et al, 2006	N=60, whole breast	Beclomethasone dipropionate spray vs no intervention	Corticosteroid group with significantly reduced incidence of moist desquamation
Omidvari et al, 2001	N=51, chest wall	Betamethasone 0.1% vs placebo vs no intervention	Steroid arm with significantly delayed occurrence of ARD
Miller et al, 2011	N=176; 140, whole breast; 29, chest wall	Mometasone Furoate 0.1% vs Placebo	No difference in the mean maximum grade of radiation dermatitis

Mometasone furoate is a medium-strength topical steroid that has a low atrophogenic potential, and has demonstrated greater anti-inflammatory activity and a longer duration of action than other medium-strength topical steroids such as betamethasone (Prakash & Benfield, 1998). MF has been shown to be effective in reducing clinically appreciated radiation dermatitis and pruritus in patients who are receiving whole breast radiotherapy in several randomized trials comparing MF with a placebo emollient (Bostrom, Lindman et al. 2001; Miller, Schwartz et al. 2011). However, its applicability in patients who have undergone mastectomy and receive irradiation of the chest wall has not been established. Only one of these studies included patients who received chest wall radiotherapy but, because the sample size was so small, they were unable to draw definitive conclusions regarding the benefit of MF in this population (Miller et al., 2011). The aim of this study is to elucidate the effect of mometasone furoate versus standard of care on patients receiving post-mastectomy irradiation, specifically.

3.4 Patient-Reported Outcomes and Provider Assessment Tools for Radiation Dermatitis

Currently, the most widely used standardized method of recording provider-assessed toxicities is the CTCAE version 4. CTCAE has been shown to result in stable assessments of toxicities among practitioners (Trotti, 2003). Using this assessment tool, grade ≥2 radiation dermatitis encompasses an assessment of both the degree of erythema and desquamation, as gauged by the provider. Grade 2 erythema is defined as "moderate to brisk," and grade 2 MD is defined as "patchy, mostly confined to skin folds and creases" (CTCAE v4.03, 2009).

There is evidence that patients and clinicians differ in their assessment of the severity of subjective skin toxicities (such as pruritus) during radiation (Neben-Wittich M. A., 2011). The Skindex-16 is a tool designed to capture patient-reported assessments of subjective adverse effects. Skindex-16 is comprised of sixteen questions, which are sub-categorized into an emotional subscale (six questions), a functional subscale (five questions), and a symptom subscale (five questions). Rankings of the questionnaire are then averaged to obtain a score of severity of patient-reported outcomes. This allows providers to gauge which aspects of the patient's experience are most affected by the treatment.

The Fitzpatrick Skin Classification is a well-recognized tool for patients' initial assessment of their general level of skin sensitivity. The scale ranges from category I to VI, representing a range from pale skin/always burns to dark skin/never burns (Fitzpatrick TB, 1988).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a Phase III double-blinded, randomized trial. Its purpose is to compare MF 0.1%, a steroid cream, with standard emollient skin care, Eucerin, on the prevention of acute grade 2 or higher skin toxicities in breast cancer patients receiving PMRT to the chest wall and regional lymph nodes. We hypothesize that MF will prevent moderate to severe radiation dermatitis in women undergoing chest wall irradiation for breast cancer.

4.2 Intervention

Eligible patients will receive skin care according to their randomization assignment during radiation therapy. Skin toxicity assessments and assessment of patient-reported compliance will be done on a weekly basis while the patient is receiving RT, by the RN or physician utilizing CTCAE 4.0 and the weekly status check form, as per current standard practice. Patient-reported skin toxicities will be measured using the Skindex-16 assessment tool. Patients will report Fitzpatrick Skin Category at the time of the History and Physical.

Patients will be followed at 10-14 days after the completion of treatment during which time they will have a provider skin assessment and they will complete an additional Skindex-16 Assessment.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Mometasone Furoate

Class: Anti-inflammatory agents
ATC Class: D07AC13
VA Class: DE200
Chemical Name: 9α,21-dichloro-11β,17-dihydroxy-16α-methyl-17(2-furanylcarbonyl)pregna-1,4-diene-3,20-dione
Molecular Formula: $C_{27}H_{30}Cl_2O_6$
CAS Number: 83919-23-7
Brands: Elocon

Topical MF is a medium-potency corticosteroid that modifies the body's immune response by suppressing the formation, release, and activity of endogenous mediators of inflammation, including prostaglandins, kinins, histamines, liposomal enzymes, and the complement system. It is available in a 0.1% cream, lotion or ointment form. Indications for topical use include relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. MF has a low atrophogenic potential, and a longer duration of action than other topical steroids in its class.

5.2 Eucerin Original cream

Eucerin Original is a hydrous lanolin emollient skin cream, which is used to soften and moisturize the skin. Emollients may be used as lubricants to treat or prevent dry, itchy skin, and minor skin irritations.

5.3 Skindex-16 Assessment Module

The usefulness of patient-reported outcomes as an alternate means to measure side effects has been reported in the literature (Huschka, Mandrekar et al. 2007). The Skindex-16 is an analog scale of symptoms and functional endpoints related to skin toxicity that can occur in the treatment area, and has been assessed for reliability: scale scores were reproducible after 72 hours, and demonstrate both content and construct validity (Chren, Lasek et al. 2001). It has been used for patients to rate skin conditions that have occurred within the previous week. It consists of a short 16-item assessment completed by the patient, using numerical analogue scales (0 = never bothered to 6 = always bothered). Responses to the Skindex-16 are categorized into three subscales: symptom, emotional, and functional (Appendix 1).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Age ≥18 years
- Stage 1-3 invasive breast cancer that is histologically confirmed at MSKCC
- Status post mastectomy with axillary exploration (sentinel node biopsy and/or axillary lymph node dissection) to receive PMRT
- ECOG Performance Status of 0 or 1

6.2 Subject Exclusion Criteria

- Male
- Patients with distant metastasis or locally recurrent breast cancer
- Patients who are pregnant or breastfeeding
- Prior radiation therapy to the ipsilateral chest wall or thorax
- Patients requiring a chest wall boost
- Concurrent chemotherapy (biologic agents are allowed)
- Psychiatric illness that would prevent the patient from giving informed consent
- Inability or unwillingness to comply with skin care instructions and follow-up
- Allergy to either Eucerin or MF• Residual grade >1 skin toxicity, cellulitis, or incompletely healed wound(s) at intended site of study drug application at simulation
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus, or connective tissue diseases (lupus, systemic sclerosis, or other collagen vascular diseases)
- Treatment with non-standard, inverse-planned Intensity Modulated Radiation Therapy (IMRT), palliative or pre-operative radiation

7.0 RECRUITMENT PLAN

All female patients who received a mastectomy and plan to receive PMRT at MSKCC will be eligible for screening. Potential participants will be identified by the protocol investigators or the departmental breast research team.

Approximately 120-150 breast cancer patients receive PMRT in the Department of Radiation Oncology in the Main Campus per year. On average, 15-20 mastectomy patients are under treatment at any moment, thus providing a large pool of patients who could be eligible for this study. We estimate treating 70-80 eligible patients at the Main Campus per year, which would enable us to reach our accrual goal of 143 patients within 3years.

8.0 PRETREATMENT EVALUATION

The History and physical exam in Radiation Oncology will include information on race/ethnicity, age, body mass index, chemotherapy status, hormone therapy, smoking history/status, diabetes, high blood pressure, Eastern Cooperative Oncology Group (ECOG) performance, and reconstruction status.

Radiation Treatment Planning will be approved by the treating MD, in order to determine type of chest wall radiotherapy (photons vs electrons) to be administered, as outlined in section 9.1.

Baseline Provider Skin Toxicity Assessment will be done within 14 days prior to the start of RT.

Patients will complete a baseline Skindex-16 Questionnaire and Fitzpatrick Skin Classification within 14 days prior to the start of RT (Appendix 1 and 2).

9.0 TREATMENT/INTERVENTION PLAN

9.1 Skin Cream Application

Arm 1 consists of patients randomized to standard of care arm (Eucerin) and Arm 2 is the experimental arm (MF 0.1%). Patients will start applying the agent to the chest wall twice daily beginning on the first day of radiation treatment and continuing 10-14 days post-completion of RT.

Patient education regarding amount to be applied (amount depending on body habitus) and area of treatment field will be reinforced by the R.N. prior to the first radiation treatment. Patients will be instructed to apply cream to the upper outer quadrant, upper inner quadrant, lower outer quadrant, and lower inner quadrant, as well as irradiated nodal fields. They will be instructed to apply cream in a thin, uniform layer twice a day, in the morning and evening, and not within the immediate 4 hours prior to radiation treatment. Patients will be informed that application immediately following radiation treatment is acceptable for those scheduled to receive morning treatments.

Patients will be instructed to wash the area daily using a mild soap such as Dove or Cetaphil, and to pat skin dry prior to cream application. Patients will be instructed to avoid the use of any exfoliating agents, such as loofah, sponges, or scrubs. Skin will not be washed for at least 8 hours after each application.

Patients will be instructed to wear soft, loose clothing to cover the treated areas, but not to use any occlusive dressings, and to avoid exposure to the sun. The use of sunscreens should be discouraged, with a preference to using clothing to cover the treatment area when exposure to the sun is expected. Patients will be discouraged from scratching the treated area and using possible skin irritants such as aftershaves, colognes, and perfumes. Aluminum-free deodorants will be permitted. Topical and/or systemic treatments for prophylaxis of dermatitis other than assigned cream will be prohibited during the study.

The topical agents will be blinded and dispensed after randomization at patient's simulation visit or at the radiation setup in 130 gram jars labelled with patient's name and MRN by the Memorial Sloan-Kettering Cancer Center (MSKCC) pharmacy. It is estimated that the average patient will require approximately 3 grams of cream per application, and will require one additional prescription for a jar of study cream during the 7 week trial. During weekly assessment of compliance at routine status check, date of dispensation of second jar will be recorded on provider assessment sheet as an additional indicator of compliance.

Patients will return to clinic for a follow up visit at 10-14 days following the completion of RT. At this visit the study investigator will perform a skin assessment and the patient will complete the Skindex-16.

9.2 Chest Wall Radiotherapy

The radiation treatment included in this study represents the institutional standard of care and is not influenced by the patient's decision to participate in this study. Either photons or electrons will be used for the primary radiotherapy treatment, depending on reconstruction status of the patient. Patients without reconstruction reveive electrons directed en face to

the chest wall with customized bolus, or photon tangents with daily bolus over the chest wall. Patients who have a reconstruction are treated with two tangential photon beams and bolus over the reconstructed breast everyday. Treatment breaks necessitated by severe toxicities will be recorded and will not be considered deviations.

Concurrent delivery of chemotherapy will not be allowed. Biologic agents and hormonal therapy during radiation will be permitted.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation During Radiation

Weekly status checks including assessment of patient compliance and Provider Skin Toxicity Assessments using CTCAE 4.0 during radiation treatment will be performed according to standard practice in the Department of Radiation Oncology. The patient will complete the Skindex-16 form during the last week of RT (week 5). The amount of topical agent used will be evaluated based on timing of patient's request for refillby an R.N. in order to assess compliance with the treatment regimen and will be documented on the Provider Skin Toxicity Assessment form.

10.2 Evaluations After Radiation

Follow-up visits will be completed 10-14 days after the completion of RT. At this time, provider assessment of skin toxicity will be performed by the physician and RN, and the patient will complete another Skindex-16 form.

Tests and Observations	Consultation	Simulation	Set-Up/ Treatment #1	During Treatment (5 weeks)	10-14 Days Following Completion of Treatment (CoT)
History and Physical	X			Weekly Status checks	
Radiation Treatment Plan approval		X			
Randomization		X			
Patient Teaching and Administration of Topical Agent		X	X	Assess compliance weekly	
Provider Assessment of Skin Toxicity		X		Provider assessment weekly	X
Patient Assessment of Fitzpatrick Category (Appendix 2)		X			
Patient Assessment of Skin Toxicity (Appendix 1)		X		Week 5 only	X

11.0 TOXICITIES/SIDE EFFECTS

The patient will be monitored for erythema and desquamation in the radiation field, which are expected side effects from chest wall radiotherapy. Some patients may develop moist desquamation, which usually heals within a few weeks and is treated with Silvadene cream and/or hydrocolloid dressings. Treatment breaks secondary to severe acute skin toxicities and/or cellulitis during radiation are not anticipated.

If a patient develops grade 2 or greater moist desquamation, or adverse reaction to the topical agent, she will be instructed to discontinue study cream and will receive standard of care management as determined by the patient's provider. These patients will continue to be evaluated according to study guidelines, and intervention will be noted on the Provider Skin Toxicity Assessment form. Patients who develop grade 2 erythema without the presence of moist desquamation will continue to use study cream without deviation from protocol guidelines.

Side effects from MF are uncommon. In controlled clinical studies of MF, the incidence of adverse reactions of burning, pruritus, and skin atrophy was 1.6%. Infrequent side effects include irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, secondary infection, striae, and miliaria. Systemic absorption may produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing syndrome, hyperglycemia, and glycosuria.

Eucerin Original side effects are rare but include skin redness, irritation, and itching.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Assessment of Primary Objective

The grading of skin toxicity will be based on the CTCAE version 4.0 scale as defined in section 3.4. To ensure unbiased skin toxicity measurement, both the clinical team and patient will be blinded to the treatment assignment. The type of skin toxicity (moist desquamation or grade ≥2 erythema), maximal score, its location within the target (chest wall or axilla), and time to occurrence will be recorded weekly during RT and at week 2 follow-up on the Provider Skin Toxicity Assessment Form. Following the post-treatment visit, the patient will not need to return to the clinic for other follow-up visits unless otherwise specified by the treating physician.

12.2 Assessment of Secondary Objectives

The Skindex-16 module score will be utilized to assess patient-reported toxicities at baseline, during week 5 of RT, and 10-14 days post-RT.

The maximal reported toxicity score and time to occurrence will be assessed weekly and at the two week follow up.

13.0 CRITERIA FOR REMOVAL FROM STUDY

It will be made clear to all participants that they are allowed to withdraw from the study at any time. If at any time the patient is found to be ineligible from the protocol as designated in the section on Criteria for Patient/Subject Eligibility, the patient will be removed from the study.

14.0 BIOSTATISTICS

This is a double-blinded, randomized trial (see Section 15.2 for details of randomization) to compare MF 0.1% cream with standard skin care (Eucerin) on the prevention of moderate to severe skin toxicities in breast cancer patients receiving post-mastectomy radiation to the chest wall and regional lymph nodes. A patient is deemed to have developed skin toxicity if she has a grade ≥2 skin toxicity as defined in Section 3.4 within 7 weeks from the beginning of radiation.

Based on estimates provided by radiation oncologists at our institution, the rate of grade ≥2 toxicity using Eucerin as skin care for chest wall radiation is ≈ 50%. This estimate is slightly lower than the findings from the Spierer study cited in section 3.2, to reflect this study's inclusion of patients treated with photons (in the presence of reconstruction) as well as electrons. We expect that the usage of MF can reduce this rate to 25%. 124 evaluable patients are needed for the comparison, with 62 patients in each arm. Two-sample, two-sided proportion tests will be used to derive the statistical significance. One interim analysis will be conducted when 31 patients in each arm have been enrolled and evaluated using the O'Brien-Flemming procedure, which will declare significance if the test p-value is less than 0.005. Correspondingly the final analysis will declare significance if the test p-value is less than 0.048. This design has a power of approximately 0.83 (i.e., detecting the true toxicity rate of 25% or lower) at the type I error (i.e., declaring MF more effective while it yields the same toxicity rate as Eucerin) rate of 0.05 based on 100000 statistical simulations.

All deaths unrelated to the toxicities, and patients lost to follow-up (before toxicities can be evaluated), will be excluded from the comparison and new patients will be accrued for replacement. To this end we plan to enroll an additional 15% of patients. Therefore our final proposed accrual is about 143 patients, which is expected to be done in 3 years.

Patient-reported skin symptoms will be scored from the Skindex-16 surveys and compared between interventions using Wilcoxon tests at each separate assessment time point. Analysis of covariance may also be used when the baseline information is taken into account as a covariate. Multiple comparison tools will be employed to adjust for statistical significance levels. Maximum reported skin toxicities will be tabulated and summary statistics will be provided. Time to occurrence of skin toxicity will be handled by routine survival analysis such as Kaplan-Meier estimation, log-rank tests, and/or Cox regression models when comparisons are needed.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Randomization will be done at MSKCC. Patients will be randomized to the MF 0.1% cream arm or the standard skin care arm with Eucerin at the ratio of 1:1. For patients enrolled at MSKCC, after eligibility is established and immediately after consent is obtained, the RSA will register participants in the PPR system and randomize participants using the Clinical Research Database (CRDB), by calling the MSKCC PPR Office at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday to Friday. Randomization will be accomplished by the method of random permuted block, and will be stratified by the presence of breast reconstruction and BMI. After treatment arm is determined by randomization, RSAs at MSKCC will notify the research staff of the participant ID via email within 24 hours of randomization. Since this is a double blind study, the research participants' treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs.

15.3 Blinding

Study drug containers will appear identical with assigned numbers divided evenly between study drug and control. Details of which drug is associated with each number will be recorded in a logbook. When a patient is assigned to a treatment arm based on the process outlined in section 15.2, the pharmacist will obtain a number assignment from CRDB, re-label the cream and keep a log recording the number of the jar dispensed.

16.0 DATA MANAGEMENT ISSUES

An RSA will be assigned to the study, whose responsibilities will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations and follow-up, will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSKCC were approved by the National Cancer Institute (NCI) in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSM Plans can be found on the MSKCC Intranet at http://mskweb2.mskcc.org/irb/index.htm.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs: the Data and Safety Monitoring Committee for Phase I and II clinical trials, and the Data and Safety Monitoring Board for Phase III clinical trials, reporting to the Center's Research Council and Institutional Review Board (IRB).

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., National Institutes of Health sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

The procedures involved in this study are felt to be of minimal risk, meaning that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The benefit derived from the study would be prevention of moderate to severe skin toxicities in breast cancer patients undergoing chest wall radiation. Patients or their legal guardians will receive comprehensive explanation of the proposed treatment options being offered on this protocol, including the nature of the investigation, rationale, alternative treatments and any known previously observed side effects, the investigational nature of the study, and the potential benefits and risks of the intervention. Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

1. Skindex-16 Form
2. Fitzpatrick Skin Classification System and CTCAE Version 4 Scoring Schema
3. Digital Photographs