

Randomized, Prospective, Open-label Phase III Trial Comparing Mebo Ointment With Biafine Cream for the Management of Acute Dermatitis During Radiotherapy for Breast Cancer

Fady B. Geara, MD, PhD,* Toufic Eid, MD,* Nicolas Zouain, MD,†
Ranim Thebian, MD,* Therese Andraos, MD,‡ Chirine Chehab, MPH,*
Paul Ramia, MD,* Bassem Youssef, MD,* and Youssef H. Zeidan, MD, PhD*

Purpose: Acute radiation dermatitis is a common side-effect of radiotherapy in breast cancer and has a profound impact on patients' quality of life, due to pain and discomfort. The aim of this study is to compare the effect of β -sitosterol (Mebo) ointment to trolamine (Biafine) cream for the prevention and treatment of radiation dermatitis in breast cancer patients receiving adjuvant radiation therapy.

Materials and Methods: This is a prospective open-label randomized phase III study developed to assess the efficacy of 2 topical agents used for management of acute radiation dermatitis. Female breast cancer patients who needed a course of radiation therapy in our institution were enrolled and randomized into 2 groups 1 with Mebo ointment and 1 with Biafine cream. Both medications were applied twice per day during the whole period of treatment and skin reactions and related symptoms were assessed weekly during the entire course. Grading of skin reactions was done according to the Radiation Therapy Oncology Group grading system.

Results: Between September 2015 and May 2017, a total of 161 patients were recruited for this trial. Mean age was similar for both groups (50.19 ± 12.57 vs. 51.73 ± 11.23 , respectively, $P=0.41$). All other patients and treatment characteristics were similar in both groups, except for the use of boost (82.7% in the Biafine group vs. 36.7% in Mebo group, $P=0.012$). Analysis was done for reactions recorded before the beginning of the boost and for the entire course including the boost. Using univariate and multivariate analysis, there was no significant difference in grades 2 and 3 dermatitis between the 2 groups. However, the incidence of severe pruritus and severe local skin pain were both significantly reduced in the Mebo group (14.1% in Biafine vs. 2.9% in Mebo, $P=0.016$ for pruritus and 11.5% vs. 1.4%, respectively, $P=0.02$ for severe pain).

Conclusions: This study showed no difference between Mebo and Biafine in the incidence and severity of breast skin dermatitis during radiation therapy. However, the use of Mebo ointment was associated with decreased severe pruritus and pain which could positively affect patient comfort and quality of life.

Key Words: breast cancer, dermatitis, radiation therapy

(*Am J Clin Oncol* 2018;41:1257–1262)

From the *Department of Radiation Oncology, American University of Beirut Medical Center; †Department of Radiation Oncology, Clemenceau Medical Center, Beirut, Lebanon; and ‡Department of Radiation Oncology, Cleveland Clinic Florida, Weston, FL.

The authors declare no conflicts of interest.

Reprints: Fady B. Geara, MD, PhD, Department of Radiation Oncology, American University of Beirut Medical Center, Bliss Street, Beirut, Lebanon. E-mail: fg00@aub.edu.lb.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0277-3732/18/4112-1257

DOI: 10.1097/COC.0000000000000460

Radiation therapy is a common treatment modality for many cancer patients with ~75% of oncology patients receiving radiation therapy as part of curative or palliative care.^{1,2} The goal of radiotherapy is to eradicate tumor cells while minimizing damage to normal tissue. However, normal cells in the radiation field may also be damaged by radiation exposure. Radiation released free radicals can damage cellular DNA, alter proteins carbohydrates and lipids which can cause local inflammatory process and cytokine release and result in structural skin damage. Typically, normal tissues have a high capability of self-repair, but repetitive radiation exposure creates an imbalance of tissue damage and repair.^{3,4}

Skin is relatively radiosensitive and tends to get affected after certain doses of radiation therapy.⁵ Early radiation skin reactions can occur within 1 to 4 weeks of treatment and may persist for 2 to 4 weeks after radiation is completed.⁶ Skin dermatitis affects about 95% of patients receiving radiation therapy but the large majority would have moderate to severe skin dermatitis making it the most common acute side effect.⁷ Skin toxicity can range from mild erythema to severe wet desquamation, and the severity of dermatitis can be assessed using various scoring systems. The most commonly used are the National Cancer Institute Common Toxicity Criteria-Adverse Event (NCI CTCAE) and the Radiation Therapy Oncology Group (RTOG) toxicity scoring system.⁸

Dermatitis can be irritating to patients and can affect their quality of life. In severe cases, it can cause interruption of the radiotherapy treatment course resulting in long delays, which could affect treatment outcome. Unfortunately, physicians often tend to overlook or underestimate radiation dermatitis unlike patients who have frequent complaints as this affects their daily activities.⁹ Many studies have investigated the use of topical agents to help preventing this skin side effect but none has shown a clear benefit to be used as standard of care.^{10,11} Trolamine emulsion (or Biafine) is largely used in clinical practice for radiation dermatitis especially in European countries. Using human volunteers Biafine was found to improve dermal healing by altering cytokine release and macrophage migration. RTOG 97-13 compared Biafine with best supportive care (BSC) in acute radiation dermatitis for women with breast cancer. Although no overall differences were noted, the study reported significant benefit for Biafine in large-breasted women. Using human skin model, others have shown that application of Biafine post-irradiation reduced vasodilatation and dermal edema, and improved epithelial proliferation. However, another phase III trial showed no advantage for the use of trolamine in reducing the incidence of grade 2 or higher radiation dermatitis in head and

neck cancer patients.¹² These results warrant further studies to improve management of radiation dermatitis. Moist Exposed Burn Ointment (Mebo; Julphar-Gulf Pharmaceutical Industries, UAE) is a herbal formulation containing β -sitosterol, as active ingredient in a base of beeswax and sesame oil. It provides optimum moisture which improves keratinocyte migration and interaction with growth factors and several studies have shown significant clinical benefit in skin burns and postoperative wound healing.^{13–16} This study was designed to compare Mebo with Biafine in the prevention and treatment of skin dermatitis in breast cancer patients receiving adjuvant radiation therapy.

MATERIALS AND METHODS

This study included breast cancer patients presenting to the Department of Radiation Oncology at the American University of Beirut Medical Center (AUBMC) to receive radiation therapy between November 2015 and May 2017. To be eligible patients must be 18 years or older, with a diagnosis of female breast cancer treated with either lumpectomy or mastectomy, and planned to receive at least 3 continuous weeks of external-beam radiotherapy to the whole breast or chest wall. Intensity-modulated radiotherapy (IMRT/IGRT) planning and delivery, conventional radiotherapy, or 3-dimensional radiotherapy techniques were all allowed. Electron boost radiation is allowed. Patients who were treated with chemotherapy should have had terminated their chemotherapy at least 2 weeks earlier. Hormonal therapy during radiation was allowed. Patients were excluded if they had history previous radiation therapy in the same area, they had severe and delayed wound care issues, have history

of allergy to either drug, pregnant, or nursing, or with severe general health problems, poor performance status (ECOG > 3), or reduced cognitive ability. No other concurrent topical agents (eg, lotions or ointments) to radiotherapy field during study treatment. Patients provided written informed consent before the start of the treatment and the study was approved by the Institutional Review Board (IRB) at the American University of Beirut (AUB).

Patients were randomized into 2 groups, 1 that received Mebo ointment and 1 that received Biafine cream (Fig. 1). Patients were provided with the cream at the beginning of their radiation therapy. Participants were asked to apply the cream twice per day on the irradiated area of the skin daily during the whole period of their treatment and for 2 weeks postend of the radiation therapy. Patients were instructed not to apply the cream before their morning radiation session to avoid compromising the radiation dose received by the breast and were also asked not to use any other lotion or cream and to avoid sun exposure at the irradiated area. Participants were assessed weekly during their treatment. The primary outcome measured was the dermatitis grade that was evaluated based on RTOG criteria.⁸

Pain and pruritus were also assessed as secondary outcomes. For simplicity, pruritus was classified as none, mild, or severe as reported by patients. Patients were also asked to score their pain out of 10. The grade of pain severity was defined as grade 1 with score up to 2.5/10, grade 2 with score 2.5 to 5/10, grade 3 with score 5 to 7.5/10, and grade 4 with score 7.5 to 10/10.^{17,18} If the dermatitis was severe enough and not responding to the assigned cream, patients were switched to

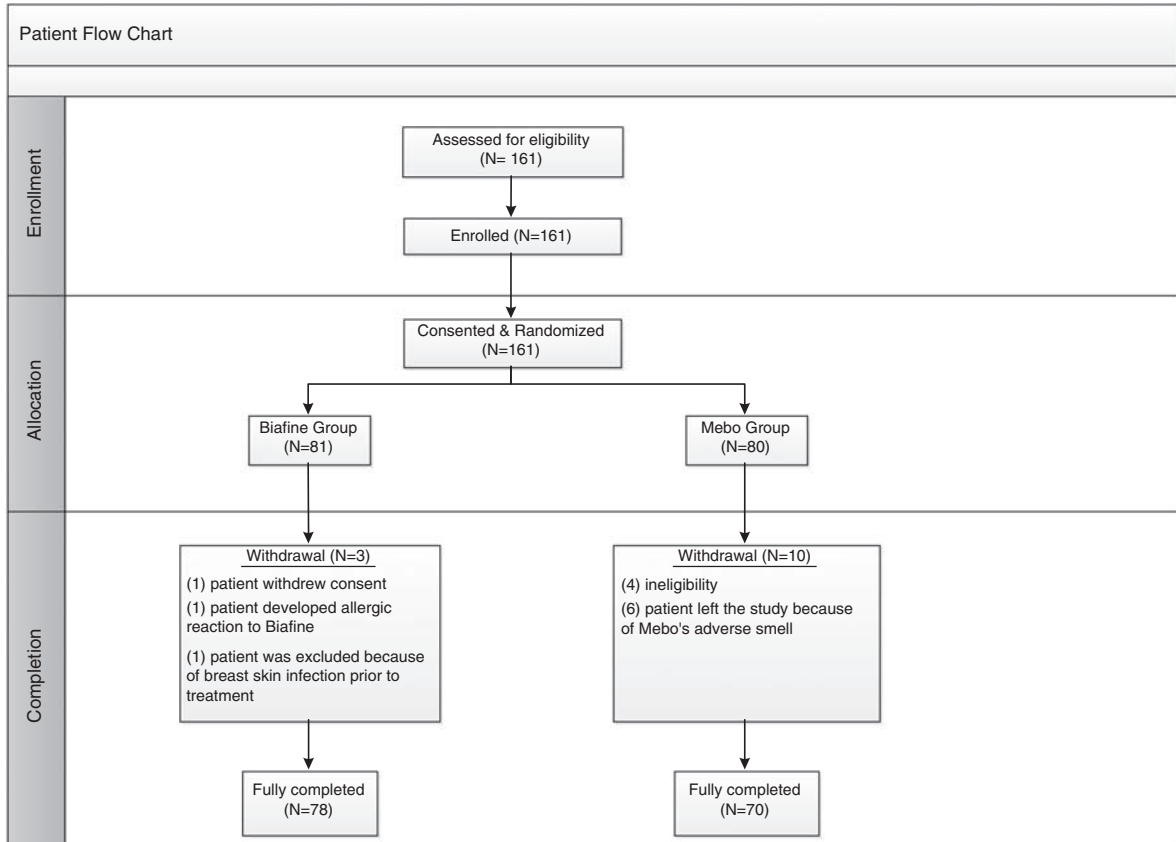


FIGURE 1. Patient flow chart for the clinical trial.

Downloaded from http://journals.lww.com/amjclinicaloncology by BHDMSpHkav1ZEquum1IQN4a+kLLNEZgbsIH 04XMH0hCwWCX1AMNnYqP/IIHQH3D3D00dRv7/TSF14C3V/C1y0abgQZXdwmIKZB7Yws= on 08/28/2024

another topical cream. Neither the participants nor the researchers were blinded to the study.

Patients enrolled received either 50 Gy in 25 fractions or 40 Gy in 15 fractions using linear accelerator. Depending on the clinical indication, some patients received SCV, IMC, or AXILLA radiation and some had a boost added. The dose of the radiation was decided by the patients' radiation oncologist. Patients' characteristics were collected such as age, the side of cancer, histology, stage, the radiation dose, and field including boost, type of surgery.

Statistical Analysis

The χ^2 test was utilized to compare acute skin toxicity between different sample groups. Multivariate logistic regression was developed to assess the associations between acute toxicity, dosimetric parameters, and clinical characteristics. Statistical significance was assumed at P -value <0.05 . The highest reported grades of radiation dermatitis were compared across the treatment arms using the χ^2 test. The burden of skin toxicity from the RTOG scale was calculated as area under the curve (AUC) using all patients with at least 2 toxicity assessments during the weeks assessment period. The AUC value for each patient was calculated using the grade of skin toxicity on the vertical scale and the time of the assessment on the horizontal scale. Patient AUC values were used to calculate an average toxicity score for each treatment arm.

TABLE 1. Patients and Treatment Characteristics

Characteristic	Biafine (%)	Mebo (%)	<i>P</i> *
Age at diagnosis (mean \pm SD) (y)	50.19 \pm 12.57	51.73 \pm 11.23	0.41
Side of breast cancer			
Left	50.6	56.3	0.47
Right	49.4	43.7	
Type of surgery			
BCS	72.8	65.4	0.400
TM	27.2	33.3	
ALND			
No	51.9	50.6	0.603
Yes	48.1	48.1	
Histology			
DCIS	8.6	8.6	0.581
IDC	63	66	
ILC	13.6	8.6	
Chemotherapy			
No	29.6	30.9	0.864
Yes	70.4	69.1	
Boost			
No	17.3	34.6	0.012
Yes	82.7	65.7	
Radiation			
Hypofractionation	44.4	34.6	0.199
Regular fractionation	55.6	65.4	
ER			
Neg	17.3	14.8	0.669
Pos	82.7	85.2	
PR			
Neg	24.7	21	0.574
Pos	75.3	79	
HER2			
Neg	92.6	74.1	0.002
Pos	7.4	25.9	

**P*: χ^2 test.

ALND indicates axillary lymphnode dissection; BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; Neg, negative; Pos, positive; PR, progesterone receptor; TM, total mastectomy.

TABLE 2. Intensity of Acute Dermatitis

Dermatitis Grade	n (%)		<i>P</i> *
	Biafine	Mebo	
0	0	4 (5.7)	0.03
≥ 1	78 (100)	66 (94.3)	0.03
≥ 2	47 (60.3)	46 (65.7)	0.502
$= 3$	11 (14.1)	6 (8.6)	0.316

**P*: χ^2 test.

Imbalance in boost delivery was handled by assessing skin reaction before delivery of the boost portion of the radiation course. All statistical analysis was performed using the SPSS software 24.0.

RESULTS

Patient and Treatment Characteristics

From November 2015 to May 2017, a total of 161 patients were eligible and randomized on this study. Out of the 80 patients in the Mebo group, 10 withdrew consent out of which 6 complained of Mebo's adverse smell. In the Biafine group, only 2 patients withdrew consent (1 due to allergic reaction) and 1 was excluded due to skin infection at start of treatment. The mean age of both groups Biafine and Mebo was 50.19 \pm 12.57 and 51.73 \pm 11.23 years, respectively ($P=0.41$). Patients' characteristics were similar in both groups, except for boost delivery (82.7% in Biafine group vs. 65.7% in Mebo, $P=0.012$). Table 1 summarizes the enrolled patients and treatment characteristics.

Acute Skin Toxicity

There was no significant difference in the overall dermatitis toxicity grades in the Mebo versus the Biafine group (Table 2). Only noted significance was for the nonoccurrence of any kind of dermatitis in 5.7% of Mebo group compared with 0% in Biafine group ($P=0.03$). Multivariate analysis also indicated no correlation between grades 2 to 3 dermatitis and medication type. There was a highly significant correlation between the occurrence of grade 2 dermatitis and hypofractionation (Table 3). As compared with conventional fractionation patients receiving hypofractionated schedules had lower grade 2 dermatitis (odds ratio, 0.13; $P < 0.0001$).

Pruritus and Pain

Severe pruritus was significantly decreased in patients using Mebo as compared with those using Biafine (14.1% in Biafine vs. 2.9% in Mebo, $P=0.016$) (Table 4). There was a highly significant correlation ($P=0.01$) between the severity of pruritus and type of medication favoring Mebo ointment (Table 5).

TABLE 3. Logistic Multivariate Analysis for Dermatitis

Variable	Grade 2 Dermatitis			Grade 3 Dermatitis		
	CI	OR	<i>P</i> *	CI	OR	<i>P</i>
Medication (M vs. B)	0.65, 3.30	1.46	0.36	0.19, 1.72	0.58	0.32
Hypofractionation	0.06, 0.28	0.13	<0.0001	0.08, 1.09	0.29	0.07
Boost	0.17, 1.03	0.42	0.06	0.11, 2.70	0.55	0.46

**P*: χ^2 test.

B indicates Biafine; CI, confidence interval; M, Mebo; OR, odds ratio.

TABLE 4. Pruritus Severity

Pruritus	Biafine (%)	Mebo (%)	P*
None	46.2	41.4	0.56
Mild pruritus	53.8	58.7	0.56
Severe pruritus	14.1	2.9	0.016

*P: χ^2 test.

Pain severity was higher in the Biafine group with 11.5% of Biafine patients reporting severe pain in comparison with 1.4% in Mebo group ($P=0.02$; Table 6). This was also shown to have significant correlation in multivariate analysis ($P=0.02$; Table 7).

Because there was an imbalance in the usage of boost between both groups, we performed additional analysis at the time point before the delivery of the boost to eliminate the influence of the additional radiation dose on the degree and symptoms of dermatitis. Table 8 shows the results of this comparison, which continues to show a significant difference in severe pruritus and grade 4 pain favoring the Mebo group.

DISCUSSION

This study is a randomized phase III study comparing Biafine to Mebo in managing radiation dermatitis. Blinding was not possible due to the different texture, color, and smell of the 2 agents. Our study showed no significant difference in our primary outcome, skin dermatitis (grade 2 or higher), among patients who received Mebo ointment versus Biafine cream. However, patients using Biafine reported more severe pruritus and pain than those using Mebo.

Biafine (Johnson & Johnson) is a product from France that is commonly prescribed for patients receiving radiation therapy. A French study concluded that Biafine enhances the first stage of the healing process by recruiting macrophages, which initiates the production of granulation tissue.¹⁹ Yet, clinical trials did not support its superiority to other topical agents used in preventing radiation dermatitis.²⁰ In a multicenter randomized clinical trial, Fisher and colleagues compared Biafine with BSC in prevention of acute radiation dermatitis. BSC was defined as institutional preference with Aloe Vera and Aquaphor as top choices. No significant difference was noted in the prevention, time to, or duration of radiation dermatitis. However, the study still suggested superiority of Biafine in patients with large breast size.⁷ A similar multicenter study by Elliott et al¹² also failed to prove an advantage of Biafine usage over institutional preference agents in head and neck cancer patients. Fenig et al²¹ compared the efficacy of Biafine cream with that of Lipiderm cream (G-Pharm, Salisbury, UK) for preventing radiation dermatitis in breast cancer patients showing no significant differences between the 2 treatment groups and a control group.

TABLE 5. Logistic Multivariate Analysis for Pruritus Severity

Variable	Pruritus			Severe Pruritus		
	CI	OR	P*	CI	OR	P
Medication (M vs. B)	0.56, 2.32	1.14	0.73	0.03, 0.65	0.13	0.01
Hypofractionation	0.12, 0.49	0.24	0.00	0.07, 1.13	0.28	0.07
Boost	0.46, 2.45	1.06	0.90	0.39, 7.61	1.72	0.47

*P: χ^2 test.
B indicates Biafine; CI, confidence interval; M, Mebo; OR, odds ratio.

TABLE 6. Pain Severity

Pain	Biafine (%)	Mebo (%)	P*
0	51.3	52.9	
≥ 1	48.7	47.1	0.85
≥ 2	24.4	20	0.52
≥ 3	16.7	8.6	0.14
= 4	11.5	1.4	0.02

*P: χ^2 test.

In all the previous studies, no added benefit or harm was observed with Biafine usage in regards to radiation dermatitis management or prevention. However, a study by Pommier et al showed less grade 2 or more skin reactions in Calendula ointment in comparison to Biafine (41% vs. 63%, $P<0.001$) with less pain experienced ($P=0.03$). However, it was associated with greater difficulty in application (30% vs. 5%) that can affect compliance.²² Despite no superiority of Biafine to other topical agents, it is commonly used in our institution and region. This can be attributed to its ease of application, affordable cost, and anecdotal evidence. Mebo is a topical ointment preparation based on the methodology of moist exposed burn therapy, its main active component is β -sitosterol (0.25%) in a base of beeswax, sesame oil, and other components well known for their role in treating cutaneous ailments. The concept of moist exposed burn therapy is to expose the wound to a physiological moist environment to enhance natural healing processes, whereby keratinocytes migration, angiogenesis, and interaction with growth factors are facilitated.²³ This product is purely natural medication that does not contain any steroids, it provides in addition an analgesic effect, an antibacterial potential, anti-inflammatory, antiedema, and antithrombotic effects. This can explain the less severity of pain and pruritus observed in the Mebo arm in this study.

Several studies have proven a remarkable role of Mebo in managing wounds, ulcers, burns, and other skin condition.^{23,24} However, there are no current studies on its effect in the prevention or management of radiation dermatitis. Still, physicians tend to extrapolate evidence supporting Mebo in certain skin conditions to radiation dermatitis making it one of the most commonly prescribed ointments for patients receiving radiation therapy in the region. This raises the need to have discrete evidence on its role in radiation dermatitis in specific.

In our study, Mebo was not associated with better dermatitis outcomes as compared with Biafine; however, less pain and pruritus were noted in the Mebo arm. The analgesic property of Mebo has been supported before. A randomized,

TABLE 7. Logistic Multivariate Analysis for Pain Severity

Variable	Pain ≥ 3			Severe Pain		
	CI	OR	P	CI	OR	P*
Medication (M vs. B)	0.11, 1.05	0.34	0.06	0.01, 0.67	0.08	0.02
Hypofractionation	0.02, 0.49	0.10	0.005	0.04, 1.19	0.21	0.08
Boost	0.69, 8.74	2.46	0.16	0.67, 17.84	3.47	0.14

*P: χ^2 test.
B indicates Biafine; CI, confidence interval; M, Mebo; OR, odds ratio.

Downloaded from http://journals.lww.com/amjclinicaloncology by BHDMSfP8Kav1ZEum1IQN14a+kLLNEZgbsIH 04XMI0hCw6CX1AWN3YDFI/QH3D3OD0dRv7T5FH4C3V/C1Y0ab9GQZXdwmfKZB7Yws= on 08/28/2024

TABLE 8. Intensity of Dermatitis, Pruritus, and Pain With the Exclusion of the Boost Week

Variable	Biafine (%)	Mebo (%)	P*
Dermatitis			
Grade ≥ 2	44.9	54.3	0.25
Grade ≥ 3	5.1	7.1	0.61
Pruritus			
Mild pruritus	48.7	52.9	0.61
Severe pruritus	15.4	0	0.001
Pain			
Grade ≥ 3	16.7	8.6	0.14
Grade 4	11.5	0	0.003

*P: χ^2 test.

controlled, clinical trial highlighted this analgesic effect where Mebo was associated with greater pain relief for the post dressing assessment during the first week after burns compared with conventional treatments.²⁵ In another randomized trial, Mebo had a greater analgesic effect in the first 5 days of therapy for second-degree burns when compared with conventional treatment.¹⁴ However, 7.5% of the women enrolled on the Mebo arm withdrew due to its adverse smell, mainly attributed to the sesame oil component. Therefore, we hope that the manufacturer will take our finding into consideration for improving the product in the future.

Many factors including patients' characteristics have been shown to play a role in the development of dermatitis. Those characteristics were accounted for in the current trial. No difference among the study arms was noted, eliminating any bias in our results except for the unbalance in boost delivery. Studies have shown an association of boost with radiation dermatitis. In a randomized trial, boost was shown to be associated with more grade 2/3 dermatitis and pruritus. However, those were measured as secondary outcomes. Moist desquamation was the primary outcome measured with no association with boost noted.²⁶

To eliminate potential bias due to boost, we repeated the analysis of patients before delivery of boost. Still, we reached the same conclusion with Mebo having an advantage in terms of severe pruritus and pain with no difference in dermatitis grading. Knowing that hypofractionation was found in various studies to be associated with less skin toxicities, our data also reflected this association.²⁷ There was no difference in the percent of patients receiving hypofractionation versus regular fractionation between the 2 arms of patients.

Skin toxicity is a common challenge in breast irradiation often causing pain and psychosocial stress. The current study suggests a role for Mebo ointment in reducing pain and pruritus in patients receiving breast radiotherapy. These results warrant further investigation of Mebo and other new products in order to minimize radiation-induced cutaneous toxicities.

ACKNOWLEDGMENT

The authors thank all the patients who participated in the trial and their families.

REFERENCES

- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58:71–96.
- Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2008: a review of current American Cancer Society

- guidelines and cancer screening issues. *CA Cancer J Clin.* 2008;58:161–179.
- Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol.* 2006;54:28–46.
- Denham JW, Hauer-Jensen M. The radiotherapeutic injury—a complex ‘wound’. *Radiother Oncol.* 2002;63:129–145.
- Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:109–122.
- McQuestion M. Evidence-based skin care management in radiation therapy: clinical update. *Semin Oncol Nurs.* 2011;27:e1–e17.
- 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.
- Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys.* 1995;31:1341–1346.
- Neben-Wittich MA, Atherton PJ, Schwartz DJ, et al. Comparison of provider-assessed and patient-reported outcome measures of acute skin toxicity during a Phase III trial of mometasone cream versus placebo during breast radiotherapy: the North Central Cancer Treatment Group (N06C4). *Int J Radiat Oncol Biol Phys.* 2011;81:397–402.
- Haruna F, Lipsett A, Marignol L. Topical management of acute radiation dermatitis in breast cancer patients: a systematic review and meta-analysis. *Anticancer Res.* 2017;37:5343–5353.
- Iacovelli NA, Galaverni M, Cavallo A, et al. Prevention and treatment of radiation-induced acute dermatitis in head and neck cancer patients: a systematic review. *Future Oncol.* 2018;14:291–305.
- Elliott EA, Wright JR, Swann RS, et al. Phase III trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99-13. *J Clin Oncol.* 2006;24:2092–2097.
- Atiyeh BS, Ghanimeh G, Kaddoura IL, et al. Split-thickness skin graft donor site dressing: preliminary results of a controlled, clinical comparative study of MEBO and Sofra-Tulle. *Ann Plast Surg.* 2001;46:87–88.
- Hirsch T, Ashkar W, Schumacher O, et al. Moist Exposed Burn Ointment (MEBO) in partial thickness burns—a randomized, comparative open mono-center study on the efficacy of dermaheal (MEBO) ointment on thermal 2nd degree burns compared to conventional therapy. *Eur J Med Res.* 2008;13:505–510.
- Jewo PI, Fadeyibi IO, Babalola OS, et al. A comparative study of the wound healing properties of Moist Exposed Burn Ointment (MEBO) and silver sulphadiazine. *Ann Burns Fire Disasters.* 2009;22:79–82.
- Mabrouk A, Boughdadi NS, Helal HA, et al. Moist occlusive dressing (Aquacel(R) Ag) versus moist open dressing (MEBO(R)) in the management of partial-thickness facial burns: a comparative study in Ain Shams University. *Burns.* 2012;38:396–403.
- Paul SM, Zelman DC, Smith M, et al. Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. *Pain.* 2005;113:37–44.
- Fejer R, Jordan A, Hartvigsen J. Categorising the severity of neck pain: establishment of cut-points for use in clinical and epidemiological research. *Pain.* 2005;119:176–182.
- Coulomb B, Friteau L, Dubertret L. Biafine applied on human epidermal wounds is chemotactic for macrophages and increases the IL-1/IL-6 ratio. *Skin Pharmacology.* 1997;10:281–287.
- Salvo N, Barnes E, van Draanen J, et al. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Current Oncology.* 2010;17:94–112.
- Fenig E, Brenner B, Katz A, et al. Topical Biafine and Lipiderm for the prevention of radiation dermatitis: A randomized prospective trial. *Oncol Rep.* 2001;8:305–309.
- Pommier P, Gomez F, Sunyach MP, et al. Phase III randomized trial of Calendula Officinalis compared with trolamine for the prevention

Downloaded from http://journals.lww.com/amjclinicaloncology by BHDMSfP-HKav1ZEoum1QIN4a+kLLNEZgbsIH 04XMI0hCw6CX1AMNyoYqPjI/QH3D300dRv7TVSF4C3V/C1y0abggQZxdmfnKZBYws= on 08/28/2024

- of acute dermatitis during irradiation for breast cancer. *J Clin Oncol*. 2004;22:1447–1453.
23. Atiyeh BS, Dham R, Kadry M, et al. Benefit-cost analysis of moist exposed burn ointment. *Burns*. 2002;28:659–663.
24. Atiyeh BS, Ioannovich J, Magliacani G, et al. Efficacy of moist exposed burn ointment in the management of cutaneous wounds and ulcers: a multicenter pilot study. *Ann Plastic Surg*. 2002;48:226–227.
25. Ang E, Lee ST, Gan CS, et al. Pain control in a randomized, controlled, clinical trial comparing moist exposed burn ointment and conventional methods in patients with partial-thickness burns. *J Burn Care Rehabil*. 2003;24:289–296.
26. Paelinck L, Gulyban A, Lakosi F, et al. Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation? A randomized controlled trial. *Radiother Oncol*. 2017;122:30–36.
27. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation a randomized clinical trial. *JAMA Oncol*. 2015;1:931–941.