Melatonin for Prevention of Breast Radiation Dermatitis: A Phase II, Prospective, Double-Blind Randomized Trial

Merav A. Ben-David MD[1], Ruth Elkayam MPA RN[1], Ilana Gelernter MA[2] and Raphael M. Pfeffer MD[3]

[1]Department of Radiation Oncology, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Facully of Medicine, Tel Aviv University, Tel Aviv, Israel
[2]Statistical Laboratory, School of Mathematics, Tel Aviv University, Tel Aviv, Israel
[3]Department of Radiation Oncology, Assuta Medical Center, Tel Aviv, Israel

ABSTRACT: **Background:** Radiation-induced dermatitis is commonly seen during radiotherapy for breast cancer. Melatonin-based creams have shown a protective effect against ultraviolet-induced erythema and a radioprotective effect in rats.

Objectives: To evaluate the efficacy of melatonin-containing cream in minimizing acute radiation dermatitis.

Methods: In this phase II, prospective, randomized, placebo-controlled double-blind study, patients who underwent breast-conserving surgery for stage 0-2 breast cancer were randomly allocated to melatonin emulsion (26 women) or placebo (21 women) for twice daily use during radiation treatment and 2 weeks following the end of radiotherapy. All women received 50 Gy whole breast radiation therapy with 2 Gy/fx using computed tomography-based 3D planning. Patients were examined and completed a detailed questionnaire weekly and 2 weeks following the end of treatment.

Results: The occurrence of grade 1/2 acute radiation dermatitis was significantly lower (59% vs. 90%, $P = 0.038$) in the melatonin group. Women older than 50 had significantly less dermatitis than younger patients (56% vs. 100%, $P = 0.021$). The maximal radiation dermatitis in the study group was grade 2 in 15% of the treated patients.

Conclusions: Patients treated with melatonin-containing emulsion experienced significantly reduced radiation dermatitis compared to patients receiving placebo.

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KEY WORDS: melatonin, radiation dermatitis, breast-conserving therapy, breast radiation, radiation side effects

Radiation therapy plays a major role in the cure of women undergoing breast-conserving surgery for breast cancer by reducing both the local recurrence rate and the risk of death from breast cancer [1]. Adjuvant breast radiation is therefore recommended following breast-conserving surgery for almost all women under the age of 70 with stage 0-III breast cancer. However, radiotherapy is associated with risk of side effects. Acute side effects of radiation therapy vary depending on radiation scheduling, dose distribution, and patient-associated factors such as size of the treated breast (skin separation, which is the distance between the entry points of the treatment fields at the center of the breast, indicating body habitus), body mass index (BMI), skin color, and probably individual genetic susceptibility to radiation [2].

Dermatitis associated with radiation usually appears as erythema ranging from mild to brisk over the treated fields, followed by dry skin desquamation which may proceed to severe and wet desquamation. Symptoms associated with radiation dermatitis include pruritus, discomfort and local pain. These side effects interfere with quality of life, reduce patient compliance, and may cause treatment interruption. Currently, there is no consistent evidence showing superiority of any topical agent for preventing or treating radiation-induced dermatitis [3-5]. This study evaluates the effect of a melatonin-containing emulsion to reduce radiation dermatitis.

Melatonin is an endogenous compound synthesized by the pineal gland. It has a role in circadian rhythms and possibly sleep processes in diurnal species. Melatonin is a potent antioxidant, and in vitro experiments have shown that melatonin is 5 to14-fold more potent in scavenging hydroxyl radicals than glutathione and mannitol, respectively [6]. In vitro studies have demonstrated that melatonin reduces radiation-induced oxidative damage in cultured human skin fibroblasts [7] and has a protective effect against radiation-induced skin damage in animal models [8,9]. We therefore assessed patients receiving breast radiation after diagnosis of breast cancer in order to evaluate the efficacy of a melatonin-containing emulsion compared to placebo in reducing radiation-induced acute dermatitis. Our primary end-point was the degree of skin toxicity during and immediately after radiation, with a secondary end-point of patient-reported comfort during the study period.

PATIENTS AND METHODS

The study group comprised 47 patients with stage 0-II (AJCC version 6) [10] breast cancer who were treated at the Sheba Medical Center with whole-breast radiation therapy between March and August 2009. The study was approved by the hos-

pital's ethics committee and was registered (NCCTG-N06C4 and NCT00438659). All patients provided written informed consent before enrolment in the trial. The hospital IRB required that two women be randomized (blinded) and complete a full course of treatment with melatonin prior to beginning the full randomized part of the study, and they are therefore included in this treatment group. All statistical tests were done with and without those two patients, with no difference in the results.

PATIENT SELECTION CRITERIA

Inclusion criteria in the present trial were adult females (age > 18 years) with stage 0-II breast cancer who underwent lumpectomy and were to receive a course of whole breast irradiation to a total dose of 50 Gy with daily fractions of 2 Gy. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 was required. Exclusion criteria were diabetes mellitus, uncontrolled hypertension, and prior diagnosis of asthma, fragrance allergy or severe prior allergic reaction. Women with known connective tissue disorder or prior chest or breast radiation were also excluded and chemotherapy had to be completed 4 weeks prior to study entry.

PROTOCOL

Following randomization, melatonin-containing emulsion with a creamy appearance (Praevoskin®, PraevoMed GmbH Germany) or placebo cream (same emulsion with no melatonin) were given to the patients in unmarked 50 g packaging. Physicians and patients were blinded to the allocated arm. Patients were instructed to apply the cream twice a day over the treated breast, but not less than 2 hours prior to radiation. Patients were asked to use no other marketed or natural products during the radiation period. Baseline physician and patient questionnaires were completed at the start of radiation therapy, weekly during 5 weeks of radiation therapy, and at a follow-up visit 2 weeks after completing whole-breast radiotherapy. At each visit, the treating physician graded the appearance of the treated breast according to the RTOG CTCA version 3.0 acute toxicity scoring system [11] (ignoring the boost area for all patients), followed by a detailed questionnaire considering hyperpigmentation, erythema, dry or wet desquamation, and rash. According to the CTCA scoring system, grade 0 = none; grade 1 = faint erythema or dry desquamation; Grade 2 = moderate to brisk erythema or a patchy moist desquamation mostly confined to skin folds and creases; Grade 3 = moderate edema, confluent moist desquamation 1.5 cm diameter and not confined to skin folds; and Grade 4 = pitting edema, skin necrosis or ulceration of full-thickness dermis and may include bleeding not induced by minor trauma or abrasion.

Patients were asked to grade their subjective feeling concerning the treated breast with regard to pain, burning sensation, pruritus, tingling, stinging, roughness, dryness and softness on a scale of 1–4, with 1 noted as "none" and 4 as "over the whole treated breast." For grade 2 dermatitis or higher, the physician could prescribe topical steroids at his or her discretion.

RADIATION TREATMENT

All women underwent computed tomography (CT) simulation for treatment planning. CT was obtained using 0.5 cm slices with the patient lying on a breast board, with both arms raised above the head. Three-dimensional treatment plans were produced and calculated according to the ICRU 51 guidelines [12]. Of the 47 patients, 46 (96%) were treated with medial and lateral wedged 6 MeV tangential fields, and one patient was treated with a combination of 6 MeV and 15 MeV photon energy with four tangential fields to achieve appropriate homogeneity.

No elective treatment breaks were allowed during the radiation treatment. Women with stage 0 and stage I-II breast cancer had an additional boost of 10 and 16 Gy (2 Gy/fx), respectively (the boost area was not evaluated for skin toxicity).

STATISTICAL ANALYSIS

This was a randomized, double-blind phase II study. The primary end-point was to compare between the degree of dermatitis during and immediately after radiation between the two arms using the RTOG CTCA criteria, with a secondary end-point of patient-reported comfort during the study period. Based on a difference of 0.5 points in the RTOG CTCA score between the groups and a standard deviation of 0.5, with a type 1 error (α)=0.05 and power of 87%, a sample size of 20 patients in each group was required. All calculations were based on intention-to-treat analysis. Background variables (patient, tumor and treatment characteristics) between groups were compared using the *t*-test for continuous variables, and the Fisher exact test or the Pearson-chi square were used for categorical variables.

RESULTS

The study population comprised 47 patients: 26 in the melatonin group and 21 in the placebo group. All participants had an ECOG performance status of 0, median age was 54 years for the melatonin group and 55 for the placebo group (P = NS), and there were no differences in patient characteristics between the groups, as presented in Table 1. Seventy-seven percent of the patients had invasive breast cancer and 23% presented with duct carcinoma in situ (DCIS). Six patients (13%) underwent re-lumpectomy due to close (less than 1 mm) or positive margins, 11 (23%) had chemotherapy prior to their radiation treatment, and 7 (15%) received concomitant trastuzumab treatment during radiation therapy. Tumor and treatment characteristics are presented in Table 2.

Maximal grade of acute dermatitis seen in our study cohort was 2, recorded in only 15% (7 patients). For the first 4 weeks of radiation there were no differences between groups in physician-assessed skin toxicity in terms of dryness, erythema,

Table 1. Patients' characteristics

	Melatonin	Placebo	*P* value
No.	26	21	
Age, median* (years)	54	55	NS
Smoker† Yes No	 9 17	 4 17	NS
Skin color‡† Fair Dark	 18 8	 15 6	NS
Hypertension†**	2	4	NS
Body mass index* Mean Range	 24 19.6-29.5	 24 19.1-30.3	NS
Performance status*	0	0	NS
Separation (cm)* Mean Range	 20 16.3–23.4	 20 17.7–23.9	NS NS

**P* value based on *t*-test

†*P* value based on Fisher exact test/Pearson chi-square

‡Fair: red or blond hair, blue eyes, freckles; red or blond hair, blue, hazel, or green eyes; cream white, fair with any eye or hair color. Dark: brown; typical Mediterranean Caucasian skin; dark brown; Middle Eastern skin types

**Medically treated hypertension

Table 2. Tumor and treatment characteristics

	Melatonin	Placebo	*P* value
Histology* IDC ILC DCIS Other	 16 4 6 0	 12 3 5 1	NS
Right/ left*	15/11	9/12	NS
Stage at diagnosis Stage 0* Stage I* Stage II*	 6 14 6	 5 14 2	NS
No. of LN excised (mean)†	5	3	NS
Re-lumpectomy*	4	4	NS
Chemotherapy*	5	6	NS
Trastuzumab during radiation*	3	4	NS
Tamoxifen (AI)*	5 (0)	4 (2)	NS

**P* value based on Fisher exact test/Pearson chi-square

†*P* value based on *t*-test

IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, DCIS = duct carcinoma in situ, LN = lymph nodes, AI = aromatase inhibitors

tanning, swelling, rash, desquamation, bleeding, cellulitis and hyperpigmentation; however, for weeks 5–7, the interaction between time and group revealed significantly reduced dermatitis in the melatonin group ($P = 0.049$).

At the 2 week follow-up visit post-radiation, there was significantly less dermatitis in the melatonin group: 59% (13 patients) had no toxicity (grade 0) and 41% (9 patients) had grade 1/2 dermatitis vs. 11% with grade 0 (2 patients) and 90% with grade 1/2 (17 patients) in the placebo group ($P = 0.03$).

Separation, BMI, age, skin color, smoking, chemotherapy, time from surgery to start of radiation and time from end of chemotherapy to radiation, concomitant hormonal therapy or trastuzumab treatment had no effect on skin toxicity. There was no difference in the patients' weekly subjective report during radiation with regard to stinging, burning, tingling, skin roughness, dryness, softness and pain between the two study arms (P = NS for all).

Subgroup analysis showed that patients 50 years and older (9 in the melatonin group, 12 in the placebo group) who were treated with melatonin had reduced skin toxicity immediately following radiation. Specifically, all patients in the placebo group had radiation dermatitis, but only 5 patients (56%) in the melatonin group had radiation dermatitis of any grade.

Four women treated with melatonin developed local-regional cutaneous allergic reaction presenting as maculopapular rash. Two patients with grade 1 recovered spontaneously within 2 days: one patient with grade 2 treated with topical steroid ointment showed full resolution within 3 days, and the other patient who had grade 3 required antihistamine therapy and oral steroids for 2 weeks until resolution. At the end of the study, all four patients had no signs of the local reaction on their skin. Treatment was discontinued in this group according to the protocol. No allergic reactions were noted in the control group.

DISCUSSION

Although radiation-induced dermatitis has been recognized almost since the discovery of X-rays in 1895, no topical agent for treating or preventing radiation dermatitis has been shown conclusively to be beneficial and accepted as the gold standard for treatment. The present randomized phase II study demonstrated better outcome with reduced dermatitis at the end of the radiation period and immediately following radiation when using melatonin-containing emulsion in comparison to the same emulsion with no melatonin (placebo group). Subgroup analysis showed that older women and smokers had the greatest benefit from melatonin, with significantly reduced dermatitis ($P = 0.021$ and $P = 0.007$ respectively).

Several series on intact breast radiotherapy using high energy photons reported the incidence of radiation-induced dermatitis grade 2 and higher to be 30–63% [13-16]. In the current study, only 15% experienced grade 2 and no grade 3 were noted. The low toxicity profile in our study could possibly be explained by the low mean BMI and separation in our study population, as well as by the precise attention to the constraints of the ICRU 50 used. In the study by Prommier et al. [14] BMI > 25 was significantly associated with acute skin toxicity in multivariate analysis, while others refer to either high BMI or obesity as a predictive factor for higher acute toxicity

[17]. When evaluating skin toxicity in patients with 3D treatment planning and calculation, Ben-David et al. [18] found that patient weight and separation significantly influenced acute skin toxicity. Only 10 patients had BMI over 26 in our study and the mean separation length was 20 cm. Due to the 3D planning and calculation mode used in the current study, most inhomogenous areas were minimal, and when needed a complex plan with multiple fields and energy was used (one patient). Increasing dose homogeneity was correlated with better toxicity profile, as described by Ben-David et al. [18] and Tucker et al. [19]. Skin dose and homogeneity were associated with dermatitis as shown by Freedman et al. [20] in their study evaluating intensity-modulated radiation therapy (IMRT) for breast cancer. Therefore, with modern radiation techniques, it is anticipated that BMI or obesity-associated skin reactions will be reduced unless these conditions are accompanied by diabetes, itself a risk factor for dermatitis.

Smoking was not found to be a risk factor for radiation dermatitis or for delay in healing in our study, perhaps due to the small number of smokers (13 patients) overall. The study by Fisher and co-researchers [13], however, found an interaction between tobacco use and healing, with delayed healing process in smokers (regardless of treatment arm, Biafine vs. best supportive care). Furthermore, Wells et al. [17] demonstrated the highest skin toxicity following radiation in smokers.

For women older than 50, melatonin significantly reduced post-treatment side effects, as no patient treated with the cream had any toxicity at all 2 weeks after radiation. Age was not found to be an influencing factor for radiation toxicity in this study, or in others [13-15,17,21]. This effect can be attributed to the reduced frequency of mitosis that accompanies aging and lowers the replication rate. Therefore, the effect of radiation on replicating cells is minimized [22]. Following application of the melatonin, it can be hypothesized that although replication rarely occurs in older patients, the anti-oxidative effect of melatonin reduces the radiation damage. Four patients experienced allergic reaction to the melatonin emulsion. In all four the reactions resolved following discontinuation of the treatment, but two patients required steroid treatment, one locally and one orally.

In order to obtain the best description of side effects, we used two separate methods and questionnaires. One was the objective scale of the Common Toxicity Criteria for Adverse Events (CTCAE version 3.0) to evaluate skin toxicity by physician or nurse. This scale is a standardized, provider-reported and validated method; however, it is an interpretation of the patient's symptoms by the physician and is not a direct patient-reported quality of life [23]. Therefore, we added an individual patient-reported scale in order to enhance the accurate evaluation of changes in quality of life, distress and bother during radiation. No difference was reported by patients in the current study between treatment arms. Recently, Neben-Wittich et al. [24] reported the comparison of provider-assessed and patient-reported outcome in the N06C4 trial, comparing mometasone cream versus placebo during breast radiotherapy. In their assessment of the relationship between provider-assessed end-point (CTCAE) and patient-reported outcomes (PRO): Skindex-16 and Skin Toxicity Assessment Tool (STAT), they concluded that patient-reported outcome provides a more complete measure of patient experience and that development of a reliable consistent and standardized patient reporting tool is warranted. An upcoming patient-reported evaluation tool is the PRO-CTCAE from the National Cancer Institute that will be incorporated in future studies.

We acknowledge the limitations of our study as this is a single-institution trial with a relatively small number of patients. Nevertheless, although small, our phase II study did reveal significant differences between the treatment groups and may lead the way for upcoming studies to further investigate the mechanism of action and clinical use of melatonin cream.

CONCLUSIONS

Our trial demonstrated that the use of melatonin-containing emulsion during radiation resulted in reduced toxicity in the late phase of treatment and immediately following radiation, especially in women older than 50. Although very few patients experienced grade 2 dermatitis, a substantial difference between melatonin emulsion and placebo was seen. As the best skin supportive care during radiation has yet to be defined [25], these results warrant a larger study with careful stratification of pretreatment subgroups by age.

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Correspondence

Dr. M.A. Ben-David

Dept. of Radiation Oncology, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-5086

Fax: (972-3) 530-5781

email: Merav.ben-david@sheba.health.gov.il

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