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Topical Hyaluronic acid vs. Standard of Care for the Prevention of Radiation Dermatitis after Adjuvant Radiotherapy for Breast Cancer: Single-Blind Randomized Phase III Clinical Trial

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Abstract

Purpose—To determine the efficacy of an emulsion containing hyaluronic acid to reduce the development of ≥ grade 2 radiation dermatitis after adjuvant breast radiation (RT) compared with best supportive care.

Materials and Methods—Women with breast cancer who had undergone lumpectomy and were to receive whole-breast RT to 50 Gy with a 10- to 16-Gy surgical bed boost were enrolled in a prospective randomized trial to compare the effectiveness of a hyaluronic acid-based gel (RadiaPlex) and a petrolatum-based gel (Aquaphor) for preventing the development of dermatitis. Each patient was randomly assigned to use hyaluronic acid gel, on the medial half or the lateral half of the irradiated breast, and the control gel to the other half. Dermatitis was graded weekly according to the Common Terminology Criteria v3.0 by the treating physician, who was blinded as to which gel was used on which area of the breast. The primary endpoint was development of ≥grade 2 dermatitis.

Results—The study closed early based on a recommendation from the Data and Safety Monitoring Board after 74 of the planned 92 patients were enrolled. Breast skin treated with the hyaluronic acid gel developed significantly higher rate of ≥grade 2 dermatitis than did skin treated with petrolatum gel (61.5% [40/65] vs. 47.7% [31/65], $P = 0.027$). Only one patient developed grade 3 dermatitis using either gel. A higher proportion of patients had worse dermatitis in the breast segment treated with hyaluronic acid gel than petrolatum gel at the end of RT (42% vs. 14%, $P = 0.003$).

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Conclusion—We found no benefit from use of a topical hyaluronic acid-based gel for reducing the development of grade ≥2 dermatitis after adjuvant RT for breast cancer. Additional studies are needed to determine the efficacy of hyaluronic acid-based gel in controlling radiation dermatitis symptoms after they develop.

Keywords

radiation dermatitis; breast cancer; hyaluronic acid; petrolatum gel

INTRODUCTION

Adjuvant radiation is a vital component of breast cancer treatment. Breast-conserving surgery coupled with radiotherapy yields survival rates equivalent to those for modified radical mastectomy alone for patients with early-stage breast cancer (1). Skin toxicity is the most common acute side effect of radiotherapy to the breast, occurring in more than 90% of patients. The severity of the reaction varies from mild erythema to moist desquamation and occasionally ulceration. Severe reactions can compromise treatment efficacy if the treatment must be interrupted while the injury heals. Treatment-related factors including the radiation dose, fraction size, and technique can influence the severity of skin toxicity, as can patient characteristics such as breast size and geometry, genetic background, and tobacco use. One study by the Radiation Therapy Oncology Group (RTOG) showed that large- breasted women developed more severe dermatologic toxicity during radiotherapy than women with smaller breasts, and healing time was prolonged in women who smoked during radiotherapy compared with that in nonsmokers (2).

Because the risk of microscopic disease in the skin is minimal in early-stage breast cancer, protecting the skin from radiation effects is desirable in terms of minimizing discomfort to the patient and is unlikely to compromise local tumor control. Radiation dermatitis can adversely affect quality of life; hence it is important to identify strategies aimed at reducing radiation dermatitis in this patient population. No standard clinical strategy has been established for preventing radiation dermatitis. Most clinicians advocate the use of topical agents such as aloe vera gel, Aquaphor (Beiersdorf, Inc, Wilton, CT), trolamine (Biafine), or hyaluronic acid cream to limit skin irritation and infection. In the United States, best supportive care in institutional practice often includes the use of Aquaphor, a petrolatum-based ointment, as reported in two RTOG trials (2, 3). The phase III trial RTOG 97-13 found that Biafine did not reduce skin toxicity or improve quality of life compared with best supportive care during adjuvant radiotherapy for breast cancer (2).

Hyaluronic acid is a naturally occurring carbohydrate polymer that is extensively distributed throughout connective tissues and is a key element of the dermal extracellular matrix. In a pilot study, a hyaluronic acid cream protected cultured fibroblasts from radiation and oxidative free radical damage induced by hydrogen peroxide (4). A double-blind randomized clinical trial also demonstrated that use of a hyaluronic acid cream significantly reduced the incidence of high-grade radiation dermatitis in patients undergoing radiotherapy for head and neck, breast, or pelvic carcinomas (5).

The present study sought to compare the efficacy of a hyaluronic acid-based topical emulsion versus a petroleum based gel often used as best supportive care, in preventing the development of grade ≥2 dermatitis in women undergoing adjuvant radiotherapy for breast cancer. The primary endpoint was grade ≥2 skin toxicity during radiotherapy.

MATERIALS AND METHODS

Patients and Treatment

Women with Tis, T0-3, N0-2, M0 histologically confirmed carcinoma of the breast who underwent breast conservation surgery with negative surgical margins were eligible. All patients received whole breast irradiation with standard opposed medial and lateral isocentric tangent fields. Computed tomography (CT) -based simulation was used to assist with field design. An additional field to treat the supraclavicular and axillary apex lymphatics was allowed, but patients receiving treatment to the internal mammary chain with a separate field were excluded. Patients were treated using static forward-planned field-in-field, intensity-modulated radiotherapy (IMRT) technique with or without wedges to optimize dose homogeneity by reducing hot spots that are present when open fields are used (6). Patients were treated to 50 Gy in 25 daily fractions, with or without a boost field for an additional 10-16 Gy to the tumor bed with electrons or photons. The tumor bed boost field design and dose were determined by the treating physician. Exclusion criteria included use of a tissue-equivalent bolus, the presence of rashes or unhealed wounds in the radiation field, stage T4 breast cancer, planned receipt of concurrent chemotherapy with radiation (although hormonal therapy and trastuzumab were allowed), and systemic lupus erythematosus or scleroderma.

Upon confirmation of patient eligibility, a medical history was obtained and demographic data collected, including breast size and body mass index. Breast size was defined as small (bra sizes 32A or 32B, 34A or 34B, and 36A), medium (bra sizes 32C, 34C, 36B or 36C, and 38A, 38B, or 38C), or large (larger bra sizes) (2). A vertical line was outlined on the breast to be irradiated, and patients were randomly assigned to use topical hyaluronic acid, on the medial half or the lateral half of the irradiated breast, and the control petrolatum based substance was applied to the other half of the breast. Detailed instructions on gel application were given to each patient as follows. Patients were instructed to apply a thin layer of the two agents three times a day over the specified area of the breast (medial or lateral), beginning one day before the start of radiotherapy and continuing every day during the radiotherapy period. On the radiation treatment days, the agents were to be applied either more than 4 hours before the radiation was to begin, or after the radiation session was completed. Patients were instructed not to apply other topical skin care products on the designated breast unless instructed otherwise by the attending physician, and documentation of the use of other prescribed topical therapies and oral analgesics was required. Daily topical application of topical hyaluronic acid and the best supportive care gel continued until the completion of the radiation treatments or the development of grade 3 or 4 skin toxicity, defined as described below.

Study Outcomes

The treating physician was blinded as to which side of the breast was being treated with the experimental gel and which side with the control. Patients were instructed not to discuss with their treating physician which side of the breast was being treated with which agent to maintain the blinding. The treating physicians were all radiation oncologists who specialize in breast treatment. The treating physicians assessed radiation dermatitis on the irradiated breast weekly according to a modified grading scale based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (7). Grades 1, 2, 3 and 4 were as defined in the CTCAE, but three additional grades (1.5, 2.5, and 3.5) were used for cases that did not fully meet the CTCAE criteria. In addition to determining the grade of skin toxicity, the blinded physician also directly compared the two sides of the breasts during the weekly evaluations and identified the side of the breast (medial or lateral) on which the skin toxicity was more severe. Patient compliance with use of the experimental

and control agents as well as other topical products was recorded. Patients who failed to apply the gels as directed for ≥9 days during radiation were removed from the study for noncompliance. Patients who developed grade ≥3 radiation dermatitis were instructed to discontinue use of the topical agents, the treating physician was unblinded to the randomization of the gels, and the skin toxicity was managed at the discretion of the treating physician.

Statistical analysis

The study was designed to include 92 patients and had 93% power to detect a decrease in the grade ≥2 radiation dermatitis rate from 0.35 to 0.175 with a two-sided significance level of 0.05 by using McNemar's test. Bowker's test was used to compare the distribution of radiation dermatitis grade according to the CTCAE between best supportive care and RadiaPlex gel. An interim analysis was planned for efficacy using an O'Brien-Fleming stopping boundary and a nominal *P* value of 0.003 once half the patients had been treated and evaluated. A Pocock-like stopping boundary was used for the interim analysis of futility with a nominal *P* value of 0.392. Univariate analysis was performed to identify patient related factors associated with increased skin toxicity using the χ^2 test. An association was considered significant at the 5% level of significance.

RESULTS

Between August 16, 2007 and February 3, 2009, 80 patients were enrolled and randomized. Six patients were randomized but did not receive treatment: four withdrew consent before therapy, one had an alteration to her radiation plan that rendered her ineligible; and one patient delayed radiotherapy to undergo chemotherapy. Thus 74 patients completed radiotherapy and were evaluable for efficacy. Of these 74 patients, nine did not complete the study because of protocol violations or personal reasons as follows: three were "off study" before completion, two used only the control agent, one used only hyaluronic acid, two did not use the agents for more than 9 days, and one applied the agents only twice daily. All of these patients were included in the primary analysis on the intent-to-treat principle, but they were excluded from an "evaluable patients" analysis, which included a total of 65 patients.

The characteristics of the enrolled patients, all of whom were female, are listed in Table 1. The mean age was 55.4 years; 61% were Caucasian, 15% were African-American, 15% were Hispanic, and 8% were Asian. The most common tumor histology was invasive ductal carcinoma. Twenty-five patients (34%) had smoked in the past but only three (4%) continued to smoke. Twenty-seven patients (36%) had large breasts. As for treatment characteristics, nearly all patients (96%) received a boost and 96% received a total radiation dose of at least 60 Gy, with 11 (15%) receiving more than 60 Gy. Only two patients (3 %) were treated with additional supraclavicular fields.

The primary objective of the study was to determine if a hyaluronic acid-based topical agent, was more effective than best supportive care in reducing the incidence of grade ≥2 radiation dermatitis. To account for individual differences in radiation response secondary to genetic variability, each subject served as her own control, as each was to apply the experimental and control agents to the irradiated breast. The Data and Safety Monitoring Board reviewed the interim analysis of 51 patients as planned, without breaking the study blind, and then requested additional analyses after 74 of the planned 92 patients had completed the study. The blind was broken by the Board after they reviewed these 74 patients, and the study was closed at the Board's recommendation. Of those 74 patients, 65 had completed the prescribed treatments and were included in an analysis of evaluable patients.

Skin-toxicity findings are presented in Tables 2 and 3. In terms of the highest grade of radiation dermatitis experienced, 44 patients in the intent-to-treat analysis and 40 in the evaluable-patients had grade ≥2 radiation dermatitis with the experimental hyaluronic acid treatment (59% and 61%, respectively); and 34 patients in the intent-to-treat analysis and 32 in the evaluable-patients analysis had grade ≥2 radiation dermatitis with the control treatment (46% and 49%, respectively). Thirty-two patients (43%) experienced grade ≥2 dermatitis regardless of which treatment was used, and 28 (38%) had grade <2 dermatitis regardless of treatment. Twelve patients (16%) had grade ≥2 dermatitis with hyaluronic acid and grade <2 dermatitis with best supportive care; only two patients (3%) had grade ≥2 radiation dermatitis with best supportive care and grade <2 radiation dermatitis with hyaluronic acid (Table 2). The *P* value from the comparison of the distribution of dermatitis severity (grade <2 vs. grade ≥2) in all 74 patients in the two treatment groups was 0.0162, indicating that irradiated skin treated with hyaluronic acid had more severe dermatitis than areas treated with best supportive care. This significant difference held in the analysis of the evaluable patients (P=0.0265).

In addition to determining the severity of radiation dermatitis, the blinded physicians also directly compared the medial and lateral sides of the irradiated breast weekly; findings are shown in Table 3. During weeks 1-5, no difference in scores were seen in either analysis (intent-to-treat or evaluable). However, during week 6, the side of the breast treated with hyaluronic acid was scored “worse” in considerably more patients (P = 0.0027 intent-to-treat, P = 0.0090 evaluable).

Table 4 summarizes the univariate analysis performed to identify patient related factors that may be associated with increased skin toxicity. No associations were found between the severity of the radiation dermatitis and body mass index, breast size, smoking history, diabetes, hypertension, or radiation dose (Table 4).

DISCUSSION

This randomized study was designed to compare the effectiveness of a topical hyaluronic acid emulsion with a petrolatum-based ointment for preventing or minimizing radiation dermatitis during radiotherapy for breast cancer. We attempted to control for both genetic variability that may contribute to inherent differences in susceptibility to radiation dermatitis and dosimetric variations within the treated breast by having each subject use both the experimental and control agents and randomizing the side of the breast on which they were to be used. We did not find any benefit from use of the hyaluronic acid-based gel in terms of preventing or reducing the severity of radiation-induced dermatitis. In fact, the extent of dermatitis was found to be worse on the hyaluronic acid side than the control side after 6 weeks of treatment.

Preclinical studies suggest that hyaluronic acid has a key role in wound healing via its role in collagen synthesis, endothelial cell proliferation, and fibroblast migration (8, 9). A double-blind randomized trial performed in Switzerland in which a hyaluronic acid-based cream was compared with a placebo for patients undergoing radiotherapy for head and neck, pelvic, or breast carcinomas showed that application of the experimental hyaluronic acid cream reduced the incidence of radiation-induced dermatitis (5). Our results did not support this conclusion, perhaps because of differences between the two patient populations. In the Swiss trial 67% of the patients were undergoing therapy for head and neck cancer and therefore were treated with radiation doses ranging from 66 to 80.5 Gy. It is plausible that any beneficial effect from hyaluronic acid is evident only for patients being treated with higher doses of radiation. In the current randomized study of only patients with breast cancer, the hyaluronic-based gel was not effective in reducing radiation dermatitis relative to

a petrolatum-based ointment. Our findings are similar to those of a phase III randomized trial conducted in France in which a hyaluronic acid cream (Ialuset, Laboratories Genevrier) was compared with a simple emollient (Topicrem) for the management of radiotherapy-induced skin toxicity in patients with breast cancer and grade 1 radiation dermatitis; no benefit for hyaluronic acid was demonstrated over the control cream (10).

Treatment technique, breast size, body mass index, and smoking history can affect the risk of acute radiation-induced skin toxicity after whole breast radiotherapy (11). In this study, we found no associations between dermatitis and body mass index or breast size, regardless of the treatment received. Other patient-related factors including history of tobacco use, hypertension, and diabetes were also not associated with dermatitis. However, only one patient in this study experienced grade ≥3 skin toxicity, and only five women (7%) were classified as having small breasts. Therefore, the lack of association may be due to small sample size in our study.

The negative impact of radiation dermatitis on patient quality of life during whole breast irradiation has been well documented. To date no topical intervention has shown convincing evidence of effectiveness in preventing or minimizing radiation dermatitis in such patients. In terms of radiation treatment techniques, the use of breast IMRT was recently found to reduce the incidence of moist desquamation relative to use of standard opposed wedge techniques in a double-blind multicenter phase III trial (12). Patients in the current study were treated with stable, multi-leaf forward-planned IMRT, a technique that produces better dose homogeneity than conventional wedged fields (6, 13). Indeed, in the standard-treatment arm of the multicenter IMRT trial, 37% of patients experienced grade 3-4 toxicity (NCI CTC 2.0). By comparison, only 1.4% of the patients in our study experienced grade 3 or higher skin toxicity, suggesting that the forward-planned IMRT technique may lead to significant reductions in severe radiation-induced dermatitis. Perhaps a hyaluronic-based topical emulsion would be more effective in reducing skin toxicity in patients undergoing whole breast irradiation with standard-field techniques, in which dose homogeneity may be less optimal.

In conclusion, this randomized, single-blind, placebo-controlled study of 74 women undergoing whole breast radiotherapy for early-stage breast carcinoma showed that application of a hyaluronic acid-based emulsion did not reduce the incidence or severity of radiation dermatitis as compared with best supportive care. These findings suggest topical hyaluronic acid is not beneficial for prophylaxis of radiation-induced skin toxicity. The current study was not designed to determine the therapeutic utility of hyaluronic acid as an intervention for existing radiation dermatitis, and thus additional studies are required to clarify whether hyaluronic acid aids in wound healing for patients who develop grade ≥2 skin toxicity.

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REFERENCES

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002; 347:1233–1241. [PubMed: 12393820]

2. 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. [PubMed: 11121627]
3. 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. [PubMed: 16648511]
4. Gracy, RLK.; Phelps, J. RadiaPlexRx gel protects cultured skin cells from oxidative free radical damage induced by hydrogen peroxide and by irradiation: a pilot study. Vol. SSA20-08. Radiological Society of North America; Chicago: p. 300p. 2005
5. Liguori V, Guillemin C, Pesce GF, et al. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. Radiother Oncol. 1997; 42:155–161. [PubMed: 9106924]
6. Borghero YO, Salehpour M, McNeese MD, et al. Multileaf field-in-field forward-planned intensity-modulated dose compensation for whole-breast irradiation is associated with reduced contralateral breast dose: a phantom model comparison. Radiother Oncol. 2007; 82:324–328. [PubMed: 17157944]
7. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003; 13:176–181. [PubMed: 12903007]
8. Croce MA, Dyne K, Boraldi F, et al. Hyaluronan affects protein and collagen synthesis by in vitro human skin fibroblasts. Tissue Cell. 2001; 33:326–331. [PubMed: 11521947]
9. Ellis IR, Schor SL. Differential effects of TGF-beta1 on hyaluronan synthesis by fetal and adult skin fibroblasts: implications for cell migration and wound healing. Exp Cell Res. 1996; 228:326–333. [PubMed: 8912726]
10. Kirova, YM. Hyaluronic acid versus simple emollient for managment of radio-induced toxicity: results of open label phase III trial. Association for Society of Radiation Oncology; San Diego, CA: 2010. Abstract # 2971
11. Fernando IN, Ford HT, Powles TJ, et al. Factors affecting acute skin toxicity in patients having breast irradiation after conservative surgery: a prospective study of treatment practice at the Royal Marsden Hospital. Clin Oncol (R Coll Radiol). 1996; 8:226–233. [PubMed: 8871000]
12. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol. 2008; 26:2085–2092. [PubMed: 18285602]
13. Murthy KK, Sivakumar SS, Davis CA, et al. Optimization of dose distribution with multi-leaf collimator using field-in-field technique for parallel opposing tangential beams of breast cancers. J Med Phys. 2008; 33:60–63. [PubMed: 19893692]

Highlights

- About half of patients experienced ≥ grade 2 radiation dermatitis
- Higher proportion experienced ≥ grade 2 radiation dermatitis using hyaluronic acid
- Higher proportion had worse radiation dermatitis using topical hyaluronic acid gel

Table 1

Pretreatment Characteristics

Characteristic	Patients (n=74)	
	No. of Patients	%
Age, years		
Mean	55.4	
Median	55.5	
Range	31 – 70.7	
Female	74	100
Race		
Caucasian	45	60.8
African American	11	14.9
Hispanic	11	14.9
Asian	6	8.1
Other	1	1.4
Smoking		
Never	49	66.2
Yes, quit >6 months ago	22	29.7
Yes, currently smoking or quit <6 months ago	3	4.1
Body Mass Index		
Mean	28.84	
Median	27.26	
Range	19.84 – 46.96	
Breast Size[†]		
Small	5	6.8
Medium	42	56.8
Large	27	36.5
Diabetes Mellitus		
Yes	5	6.8
Boost		
Yes	71	95.9
No	3	4.1
Dose, Gy		
<60	3	4.1
60	60	81.1
>60	11	14.9

Characteristic	Patients (n=74)	
	No. of Patients	%
Supraclavicular Field		
Yes	2	2.7
No	72	97.3

† Small=bra size 32 A,B; 34A,B; or 36A,B; medium= 32C; 34C; 36B,C, 38 A,B,C; large=any larger size

Table 2
Maximum Grade of Radiation Dermatitis

Intent-to-Treat Analysis

		Supportive Care (n=74)		
	Grade	0.0 – 1.5	2.0 – 3.0	Total
Hyaluronic Acid (n=74)	0.0 – 1.5	**28**	**2**	30
	2.0 – 3.0	**12**	**32**	44
	Total	40	34	74

Evaluable-Patient Analysis

		Supportive Care (n=65)		
	Grade	0.0 – 1.5	2.0 – 3.0	Total
Hyaluronic Acid (n=65)	0.0 – 1.5	**23**	**2**	25
	2.0 – 3.0	**11**	**29**	40
	Total	34	31	65

Table 3
Results of Side-by-Side Comparisons in Weekly Evaluations

Intent-to-Treat Analysis (n =74)					
	Supportive Care Worse	**Hyaluronic Acid Worse**	**Same**	**No Score**	***P* Value**
Week 1	1	0	62	11	0.3173
Week 2	0	1	72	1	0.3173
Week 3	4	3	66	1	0.7055
Week 4	9	8	54	3	0.8084
Week 5	11	18	41	4	0.1936
Week 6	9	27	33	5	**0.0027**

Evaluable-Patients Analysis (n=65)					
	Supportive Care Worse	**Hyaluronic Acid Worse**	**Same**	**No Score**	***P* Value**
Week 1	1	0	56	8	0.3173
Week 2	0	1	63	1	0.3173
Week 3	3	2	60	0	0.6547
Week 4	8	7	38	1	0.7963
Week 5	10	16	37	2	0.2393
Week 6	9	24	27	5	**0.0090**

Table 4

Univariate Analysis of Factors That May Be Associated with Increased Radiation Dermatitis

Factor	*P* Value
BMI (> vs. > mean)	0.126
Breast Size (small vs. medium/large)	0.483
Ever Smoker	0.615
Current Smoker	0.369
Diabetes	0.197
Hypertension	0.476
Dose (≤ 60 Gy vs. >60)	0.188

Abbreviation: BMI, body mass index