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ORIGINAL REPORT

Phase III Randomized Trial of *Calendula Officinalis* Compared With Trolamine for the Prevention of Acute Dermatitis During Irradiation for Breast Cancer

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ABSTRACT

Purpose
The effectiveness of nonsteroid topical agents for the prevention of acute dermatitis during adjuvant radiotherapy for breast carcinoma has not been demonstrated. The goal of this study was to compare the effectiveness of calendula (Pommade au Calendula par Digestion; Boiron Ltd, Levallois-Perret, France) with that of trolamine (Biafine; Genmedix Ltd, France), which is considered in many institutions to be the reference topical agent.

Patients and Methods
Between July 1999 and June 2001, 254 patients who had been operated on for breast cancer and who were to receive postoperative radiation therapy were randomly allocated to application of either trolamine (128 patients) or calendula (126 patients) on the irradiated fields after each session. The primary end point was the occurrence of acute dermatitis of grade 2 or higher. Prognostic factors, including treatment modalities and patient characteristics, were also investigated. Secondary end points were the occurrence of pain, the quantity of topical agent used, and patient satisfaction.

Results
The occurrence of acute dermatitis of grade 2 or higher was significantly lower (41% *v* 63%; $P < .001$) with the use of calendula than with trolamine. Moreover, patients receiving calendula had less frequent interruption of radiotherapy and significantly reduced radiation-induced pain. Calendula was considered to be more difficult to apply, but self-assessed satisfaction was greater. Body mass index and adjuvant chemotherapy before radiotherapy after lumpectomy were significant prognostic factors for acute dermatitis.

Conclusion
Calendula is highly effective for the prevention of acute dermatitis of grade 2 or higher and should be proposed for patients undergoing postoperative irradiation for breast cancer.

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INTRODUCTION

About 33,000 women a year in France receive a new diagnosis of breast cancer, and most are treated with radiotherapy after conservative surgery or mastectomy. In approximately 80% of patients, irradiation induces dermatitis, ranging in severity from mild to severe erythema to moist desquamation. The consequences of dermatitis are numerous and include impairment of the quality of life due to pain and interruption of treatment, which may be prejudicial to local control.[1,2]

No standard treatment has been recommended for the prevention of radiation-induced dermatitis. Keeping irradiated skin clean by washing with soap and water during radiotherapy for breast cancer seemed to prevent acute skin reactions.[3] Topical agents, such as corticosteroid creams and other products including aloe vera, Aquaphor (Beirsdorf Inc, Wilton, CT), and trolamine (Biafine; Genmedix Ltd, France), are commonly prescribed at the onset of radiation dermatitis or, in some institutions, at the beginning of radiotherapy. Corticosteroid cream was shown to be significantly more effective than an emollient cream in reducing the occurrence of acute radiation-induced dermatitis in two small randomized studies,[4,5] and

only few randomized trials have suggested the superiority of noncorticosteroid creams (hyaluronic acid cream, sucralfate cream) compared with placebo.[6,7] However, no large randomized studies demonstrated the efficacy of any local, nonsteroid topical agents in preventing radiation-induced dermatitis in postoperative breast cancer.[8-11]

A survey conducted in 2001 revealed that one third of French radiation oncologists prescribed a preventive topical agent for women undergoing irradiation for breast cancer. The agent used almost exclusively was trolamine; since 1973, it has been the only nonsteroid topical agent for which the patient is reimbursed by the national healthcare system for the indication "radiation-induced dermatitis." Trolamine is an oil-in-water emulsion that can enhance skin healing by recruiting macrophages and modifying the concentrations of various immunomodulators.[12,13] Two randomized trials, however, have failed to support a prophylactic advantage of trolamine over best supportive care or another topical agent (Lipiderm; G Pharm Ltd, France).[9,10] Trolamine was nevertheless well tolerated, and the randomized trial reported by Fisher et al[10] indicated that it was probably more effective in healing radiation-induced dermatitis than no treatment or other topical agents used in best supportive care. In a phase II study of the effectiveness of trolamine for preventing acute skin toxicity in women undergoing radiotherapy with concomitant chemotherapy, despite frequent grade 2 radiation dermatitis (83%), no treatment delays or interruptions were observed because of skin toxicity.[14]

Calendula (Pommade au Calendula par Digestion; calendula extract ointment; Boiron Ltd, Levallois-Perret, France) is fabricated from a plant of the marigold family, *Calendula officinalis*. The digest is obtained by incubation at 75°C in petroleum jelly to extract the liposoluble components of the plant. Calendula is commercialized in France for adjuvant treatment of irritant dermatitis, skin lesions, and superficial burns. In a randomized, open, parallel study with 156 patients of the effectiveness of calendula for the local management of second- and third-degree burns, it was significantly better tolerated than Elase (a proteolytic ointment; Pfizer, New York, NY) and petroleum jelly, and marginally significantly better than petroleum jelly alone for healing.[15]

The aim of this randomized phase III study was to assess the effectiveness of calendula for the prevention of acute radiation-induced dermatitis of grade 2 or higher during postoperative radiotherapy for breast cancer, compared with trolamine. The secondary objectives were to assess pain, treatment interruption as a result of skin reactions, patient satisfaction, and the quantity of the agent used. Prognostic factors for the incidence and severity of radiation-induced dermatitis were assessed and compared with literature data.

PATIENTS AND METHODS

Patients

Between October 1999 and June 2001, 254 patients in the Department of Radiotherapy at the regional cancer center, Centre Léon Bérard (Lyon, France), were randomly assigned to receive calendula (126 women) or trolamine (128 women). For inclusion, the women had to be 18 to 75 years of age with a nonmetastatic breast adenocarcinoma treated by either lumpectomy or mastectomy with or without adjuvant postoperative chemotherapy or hormonal treatment, and referred to the Department of Radiotherapy for postoperative radiotherapy. No concomitant chemotherapy was allowed. Women with bilateral or in situ breast cancer, patients who were allergic to either of the two agents, and pregnant women were excluded. Informed consent was mandatory. The protocol was approved by an ethical committee.

Methods

Standard irradiation fractionation (2 Gy per session, five sessions per week) was used. Each woman underwent a computed tomography scan to determine the energy of the x-rays and electrons, and, if necessary, wedge filters and bolus were used to optimize the dosimetry and to conform to the recommendations of the International Commission on Radiation Units and Measurements. Women who had undergone lumpectomy received 52 Gy from two tangential fields to the whole breast on a 5-MV accelerator. Women with large breasts received a maximum of 30% of the dose from 10-MV x-rays, to ensure a homogeneous delivery of the dose. A 10-Gy boost was delivered with electrons to the tumor bed. For women who had undergone mastectomy, 46 Gy was delivered to the chest wall with electrons (dose specified to the 90% isodose line), with or without a bolus, according to the dosimetry. The bolus was added at the most for two thirds of the sessions, and only for patients with previous mastectomy. Its use was not adjusted according to skin toxicity. If relevant, internal mammary and supraclavicular nodes were irradiated with mixed beams (5-MV x-rays and electrons).

Patients were asked to start topical application of their ointment on irradiated skin at the onset of radiotherapy, twice a day or more, depending on the occurrence of dermatitis and pain, until completion of their radiotherapy. The allocated agents were delivered directly to the patients by the pharmacist, in similar 100-g packaging. No other prophylactic creams, lotions, or gels were allowed. However, physicians were free to treat established dermatitis of grade 2 or higher and/or allergy as they considered appropriate. To preserve the single blinding, patients were instructed not to use the agent 2 hours or less before an irradiation session or before the treatment evaluation.

Each patient attended a consultation with her radiotherapist once a week, during which acute dermal toxicity was evaluated according to the Radiation Therapy Oncology Group (RTOG) scale at each irradiated volume: breast or chest wall and, if relevant, submammary fold, armpit, internal mammary nodes, and supraclavicular nodes (Table 1).[16] Pain was assessed each week on a 10-cm visual analog scale (VAS). The relationship between numerical ratings of pain severity and interference with daily functions for cancer patients, and the reliability of VAS to assess acute toxicity, have been demonstrated previously.[17-19] The occurrence, duration, and reasons for interruption of radiotherapy or of allocated cream application were registered, as were allergic reactions and quantity of the agent used, until the completion of radiotherapy. At the end of the study, the patients were asked to complete a

Table 1. RTOG Acute Skin Toxicity Grades

Grade				
0	1	2	3	4
No change over baseline	Follicular, faint, or dull erythema; epilation, dry desquamation, or decrease in sweating	Tender, bright erythema; patchy, moist desquamation or moderate edema	Confluent, moist desquamation other than skin folds; pitting edema	Ulceration, hemorrhage, necrosis

Abbreviation: RTOG, Radiation Therapy Oncology Group.

questionnaire to assess their satisfaction with respect to ease of application, pain, and dermatitis relief.

Statistical Analysis

Proc plan command (SAS Institute, Cary, NC) was used to generate random allocation lists with block sizes of six each. After verification of patient eligibility, the data manager of the study contacted the biostatistics unit to obtain the randomization group.

The centralized randomization was stratified according to the patient's skin type, which was evaluated on the basis of skin phenotype according to the Pathak score used in the pathology of melanoma, as grade 1 or 2 versus grade 3, 4, 5, or 6[20-22] (Table 2). Only the physician was unaware of which ointment the patients were using. A double-blind study was not possible owing to the organoleptic properties of calendula. Skin toxicity was defined as the maximal toxicity observed at all irradiated sites.

The incidence of skin toxicity of grade 2 or higher observed during breast irradiation plus preventive treatment with trolamine ointment was estimated to be 75%. The objective was to demonstrate a 20% decrease in that incidence; that is, 55% toxicity of grade 2 or higher with calendula ointment. To detect this difference with a power of 0.90 using a two-sided test at significance level 0.05, it was necessary to recruit 254 patients. All of the analyses were performed on the basis of intention to treat.

The qualitative measures were compared by the χ^2 test or Fisher's exact test, as appropriate. For quantitative measures, the Student's *t* test or Wilcoxon-Mann-Whitney tests were used. All of the *P* values are two sided.

A multivariate analysis for skin toxicity, which tested the type of ointment applied fitted on potential prognostic factors, also was performed. The first logistic regression model was applied to all patients. To test the prognostic value of bra and cup size, a second logistic regression was performed after removal of the data for the 50 patients who had undergone a mastectomy. In both models, a step-by-step elimination procedure was chosen, retaining factors with a two-sided level of significance less than 0.10.

RESULTS

Patients and Treatment

Patient characteristics are listed in Table 3. There were no significant differences between the two groups. The irradiation modalities were similar with respect to the target volumes, the type of radiation (photon, electron beam), and the use of a bolus. The dose delivered after lumpectomy was not identical in both groups ($P = .06$); 15.3% and 6% of patients, respectively, in the trolamine and calendula groups received ≤ 61 Gy.

Assessment of Acute Dermatitis and Tolerance

The incidence of acute skin toxicity of grade 2 to 3 was 41% (95% CI, 37 to 46) in the group given calendula and 63% (95% CI, 59 to 68) in the group given trolamine ($P < .001$). Nine patients (7%) given calendula and 20 patients (20%) given trolamine presented with grade 3 toxicity ($P = .034$). No grade 4 toxicity was observed. The benefit was most marked at sites at risk of maceration (submammary fold, armpit, and tangential area) and sites with thin skin, such as the subclavicular space (Table 4).

Treatment was interrupted for only one patient receiving calendula and for a reason unrelated to the radiotherapy, whereas 15 treatment interruptions were observed in the group given trolamine: 12 treatment interruptions were because of skin toxicity (9%), one treatment interruption was because of a lymphocele abscess, and two treatment interruptions were unrelated to the radiotherapy. The mean length of treatment interruption in this group was 10 days (range, 2 to 22 days). No second interruption of treatment was recorded.

Table 2. Pathak Scale: Skin Type Based on Facultative Response to Exposure to Ultraviolet Light (45-60 minutes of noonday sun)

Skin Type	Usual Skin Color	Usual Hair Color	Usual Eye Color	Sunburn	Tanning 7 Days After Exposure
1	Pale (± freckles)	Red-blonde	Blue or green	Yes, painful	Nil
2	Fair	Blonde-light brown	Blue or green	Yes, painful	Light
3	Fair-light brown	Brown	Brown	Yes, slightly tender	Moderate
4	Light brown	Brown	Brown	No	Good
5	Brown	Brown-dark brown	Brown	No	Profuse
6	Black	Dark-brown	Dark-brown	No	Profuse

Table 3. Characteristics of 254 Patients Treated With Postoperative Radiotherapy After Breast Cancer

Characteristic	Calendula (n = 126)		Trolamine (n = 128)		*P*
	Mean	Range	Mean	Range	
Age, years	56.5	28.5-74.5	55.1	26.5-74.3	.34
Body mass index	24.8	18.1-38.1	24.9	17.7-39.7	.84
Radiotherapy dose, Gy					
Mastectomy	47.6	46-52	47.2	46-50	.46
Lumpectomy	61.9	60-64	61.8	59-64	.06
	No. of Patients	%	No. of Patients	%	
Bra size, cm					
80-90	56	45	42	35	.4
95-115	41	33	54	45	
Cup size					
A-B	59	48	49	41	.35
C-E	38	31	47	39	
Skin phenotype (Pathak)					
1-2	36	29	38	30	.85
3-6	90	71	90	70	
Type of surgery before radiotherapy					
Lumpectomy	99	78	105	82	.48
Mastectomy	27	22	23	18	
Histologic type of tumor					
Infiltrating ductal carcinoma	105	83	111	87	.43
Infiltrating lobular carcinoma	10	8	11	9	
Other	11	9	6	5	
Chemotherapy before radiotherapy					
Yes	60	47	72	56	.17
No	66	52	56	44	
Use of bolus					
Yes	12	10	6	5	.13
No	114	90	122	95	

Among the 22 patients with a dose delivered ≤ 61 Gy, 16 (72%) have had a skin toxicity of grade 2 to 3.

No allergic reactions were observed in the group given calendula, whereas four patients given trolamine developed allergic-type reactions (pruritis and urticaria).

The mean maximal pain evaluated on the VAS was 1.54 (95% CI, 1.20 to 1.89) in the group given calendula and 2.10 (95% CI, 1.72 to 2.48) in the group given trolamine ($P = .03$). Maximal pain was observed during the fifth and sixth weeks of treatment, as were maximal radiotherapy-induced dermatitis and the occurrence of treatment interruptions in the group given trolamine.

Adherence to application of the ointments throughout treatment, evaluated by the physician, was considered good for 84% of the patients given calendula and 92% of those given trolamine ($P = .047$).

The self-administered questionnaire on satisfaction was completed by 226 patients, (113 patients with each ointment). Topical application of the ointment was considered difficult by 30% of patients given calendula and 5% of those given trolamine, and two patients stopped using calendula because of that difficulty. The satisfaction of the patients with respect to prevention of erythema (69% with calendula; 39% with trolamine) and pain (65% with calendula; 46% with trolamine) was strongly associated with the occurrence of dermatitis of RTOG grade 0 to 1 (59% with calendula; 37% with trolamine). The mean total number of tubes used was 2.7 for calendula and 4.4 for trolamine, equivalent to 1.62 times more trolamine than calendula.

Prognostic Factors for Acute Radiation-Induced Dermatitis

Potential prognostic factors for radiotherapy-induced dermatitis of grade 2 or higher were analyzed: age (< 55 *v* ≥ 55 years), body mass index (BMI; ≤ 25 *v* > 25), bra size (80 to 90 *v* 95 to 115cm), cup size (A to B *v* C to E), skin phenotype (1 to 2 *v* 3 to 6), sun allergy (yes *v* no), type of surgery (lumpectomy *v* mastectomy), chemotherapy before radiotherapy (yes *v* no), irradiation of internal mammary nodes (yes *v* no), irradiation of supraclavicular nodes (yes *v* no), bolus (yes *v* no), and type of ointment applied (calendula *v* trolamine).

Multivariate analysis of these factors for all patients revealed four significant variables: BMI, type of surgery, chemo-

Table 4. Correlation Between Irradiation Localization and Skin Toxicity in 254 Breast Cancer Patients Treated With Postoperative Radiotherapy

Skin Toxicity (grade)	Calendula		Trolamine		P (χ^2)
	No. of Patients	%	No. of Patients	%	
Overall					
0-1	74	59	47	37	< .001
2-3	52	41	81	63	
Breast					
0-1	78	79	75	71	.21
2-3	21	21	30	29	
Submammary fold					
0-1	65	66	52	50	.02
2-3	34	34	53	50	
Armpit and tangential area					
0-1	70	72	53	52	.004
2-3	27	28	48	48	
Chest wall					
0-1	24	89	17	79	.17
2-3	3	11	6	26	
Supraclavicular nodes					
0-1	55	72	29	37	< .001
2-3	21	28	49	63	
Internal mammary nodes					
0-1	53	86	50	74	.09
2-3	9	14	18	26	

therapy before radiotherapy, and type of ointment applied. Statistically significant interactions were found between the first three factors. Introduction of these interactions into the logistic model (Table 5) showed that the risk for skin toxicity of grade 2 or higher was significantly increased for women whose BMI was ≥ 25 ($P < .001$) and for women who had received chemotherapy before radiotherapy after a lumpectomy ($P = .01$). In contrast, skin toxicity was not increased by chemotherapy before radiotherapy in the subgroup of patients with a BMI ≥ 25. Calendula was significantly superior to trolamine in the prevention of grade 2 or higher skin acute toxicity ($P < .001$).

The multivariate analysis for potential prognostic factors for patients who had had a lumpectomy revealed three variables: chemotherapy before radiotherapy, BMI ≥ 25, and type of ointment applied. Bra size did not seem to be an independent major risk factor ($P = .16$) and was not integrated in the final model. The interaction between chemotherapy before radiotherapy and BMI was statistically significant, and was introduced into the analysis. The final model showed that a BMI ≥ 25 ($P < .001$) and chemotherapy before radiotherapy ($P < .001$) were risk factors for toxicity (Table 6). Type of ointment was highly significant ($P = .001$). As in the first model, no increase of skin toxicity was observed in patients with chemotherapy before radiotherapy in the subgroup of patients with a BMI ≥ 25.

DISCUSSION

This large randomized study demonstrated that a nonsteroid topical agent was significantly effective in preventing mild to severe radiation-induced dermatitis during radiotherapy for breast cancer. Calendula was statistically

Table 5. Multivariate Analysis (logistic regression) for Prognostic Factors for Skin Toxicity of Grade 2 or Higher in 254 Patients Treated With Postoperative Radiotherapy After Breast Cancer

Factor	Relative Risk	95% CI	P
Trolamine ointment	3.17	1.74 to 5.78	< .001
BMI ≥ 25	7.23	3.02 to 17.34	< .001
Lumpectomy	1.37	0.36 to 5.24	.65
Chemotherapy before radiotherapy	0.47	0.09 to 2.54	.38
Lumpectomy and chemotherapy before radiotherapy	9.25	1.7 to 50.3	.01
BMI ≥ 25 and chemotherapy before radiotherapy	0.21	0.06 to 0.72	.013

Abbreviation: BMI, body mass index.

Table 6. Multivariate Analysis (logistic regression) for Prognostic Factors for Skin Toxicity of Grade 2 or Higher in Patients Treated With Postoperative Radiotherapy After Lumpectomy for Breast Cancer

Factor	Relative Risk	95% CI	P
Trolamine ointment	3.16	1.64 to 6.09	.001
BMI ≥ 25	8.97	3.34 to 23.05	< .001
Chemotherapy before radiotherapy	4.57	2.01 to 10.39	< .001
BMI ≥ 25 and chemotherapy before radiotherapy	0.19	0.05 to 0.73	.016

Abbreviation: BMI, body mass index.

significantly superior to trolamine for the primary end point, prevention of skin toxicity of RTOG grade 2 or higher, and for all the secondary end points (including allergy, interruption of treatment, patient satisfaction for relief of pain, and dermatitis), with the exception of ease of application, which was considered by the patients to be more difficult with calendula than with trolamine. The quantity of agent used was significantly smaller with calendula than with trolamine, although this would not lead to a cost reduction, given that the price of calendula is at present twice that of trolamine.

We used trolamine as the reference treatment, even though a better effectiveness was not demonstrated in preventing radiation-induced dermatitis than best supportive care or no preventive treatment.[9,10] The main reason was that trolamine has been used routinely for several years in our institution, as in many other French radiotherapy departments. Given that most patients are urged by their surgeon and their general practitioner to use trolamine preventively, we considered that this could have led to major deviations from the protocol. Moreover, even though trolamine was not effective in preventing radiation-induced dermatitis, the randomized RTOG study strongly suggested that it might have curative properties.[10] Hyaluronic acid, sucralfate, and corticosteroid creams were not used as referent agents because the randomized trials in which they were tested accrued few patients, and the radiation sites were numerous and not homogeneous.[4,6,7]

Because of differences in texture, color, and smell, it was not possible to perform a double-blind randomized study. Simple blinding of the clinician nevertheless removed bias with respect to the main objective of the study, and the physicians were trained to grade dermatitis before the beginning of the study.

The incidence and the severity of RTOG-scale graded skin acute toxicity with trolamine in our study was significantly different than the results reported in the RTOG protocol, with 63% versus 41% grade 2 or higher and 20% versus no grade 3 skin acute toxicity occurrences, respectively.[10] The inferior rate of acute toxicity in the RTOG study could be related to an inferior total dose delivered (10% of the patients received less than 59 Gy), and to the exclusion of patients receiving chemotherapy before radiotherapy, whereas 56% patients in the trolamine arm received chemotherapy before radiotherapy in our study.

However, despite similar doses and irradiation technique, and despite the exclusion of patients with prior chemotherapy, Fenig et al[9] reported 30% grade 3 RTOG acute skin toxicity with trolamine. The incidence of grade 2 was not reported. Given that we did not find any significant value of skin types, it is likely that the differences observed mainly are due to the subjectivity in scoring acute skin reactions with the RTOG scale. However, BMI was not reported in the previous studies and could be a confounding factor.

The failure of other studies to demonstrate a preventive effect of other nonsteroid topical agents might have been due to methodological problems, especially the limited numbers of patients included.[8-10] Nevertheless, these previous studies did not suggest that the tested agents had any preventive effect.

Several prognostic factors have been proposed for radiation-induced acute and late skin toxicity: total daily dose, total delivered dose, fractionation scheme, volume of skin treated, irradiation technique, energy of the irradiation beam used (photons, electrons), dose distribution, and some individual factors.[23] Prospective studies for breast cancer irradiation revealed that semisupine position, large bra cup size, and skin complexion were significant adverse factors for acute skin toxicity.[8,10,24] Although used as a basis for stratification in our study, we did not find any significant differences according to the skin types, even when comparing high Pathak scores of 5 to 6 with scores of 1 to 4 (data not shown). The BMI was a significant factor ($P < .001$) and had a more prognostic value than the bra size.

Type of surgery was not a significant prognostic factor for skin toxicity in the entire series, but lumpectomy was strongly correlated with skin toxicity of grade 2 or more in patients previously given chemotherapy. In our experience, the use of a bolus was not an adverse prognostic factor.

We did not include the total dose in the multivariate model because this factor could be influenced directly by the acute skin toxicity occurrence. Indeed, we observed in our study that 72% of patients receiving ≤ 61 Gy had developed acute grade 2 to 3 skin toxicity.

The role of previous chemotherapy in the occurrence of radiation-induced skin toxicity was unclear. In the multivariate analysis, previous chemotherapy significantly increased the prevalence of dermatitis of grade 2 or higher among women who had had a lumpectomy, with the exception of patients with a BMI ≥ 25. We have not found similar observations in the medical literature.

In conclusion, calendula was statistically significantly more effective than trolamine in preventing acute dermatitis grade 2 or higher during adjuvant postoperative breast irradiation. The clinical relevance of this finding is emphasized by the significant improvement in self-assessed patient satisfaction with regard to pain and dermatitis. Calendula should be proposed as preventive treatment for patients undergoing postoperative irradiation for breast cancer.

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The authors indicated no potential conflicts of interest.

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