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Research Paper

Evaluation of the effect of topical agents on radiation-induced skin disease by reflectance spectrophotometry

Luisa Rizza[a], Antonio D'Agostino[b], Andrea Girlando[b] and Carmelo Puglia[a]

[a]School of Pharmacy, University of Catania, Italy and [b]Department of Radiotherapy, Humanitas Centro Catanese di Oncologia, Catania, Italy

Abstract

Objectives Radiotherapy may cause severe skin changes that significantly interfere with the patient's quality of life and reduce radiotherapy effectiveness. Many skin care instructions and various topical agents are recommended to help patients in the management of radiation skin reactions, but evidence to support the value of the topical treatments of the irradiated skin is lacking. In the present study we investigated the effects of topical agents used as supportive care to minimise radiation-induced skin disease using an instrumental method.

Methods Subjects who were undergoing a planned course of radiation therapy after breast-conserving surgery were randomised to treatment (using one of two topical agents) or non-treatment (control) groups and monitored over 8 weeks. The intensity of skin erythema was evaluated once per week by non-invasive instrumental reflectance spectrophotometry in comparison with a visual scoring system.

Key findings Examination of the erythema time course by a sensitive spectrophotometric reflectance method showed a significant increase of skin reactions in the non-treated group after the second week of treatment and maximal alterations between the fourth and sixth week.

Conclusions From the results obtained, we observed that application of topical agents used in radio-induced skin disease were able to significantly reduce the erythema extent compared to the non-treated group.

Keywords radiation skin reactions; reflectance spectrophotometry; supportive care; topical agents

Introduction

Breast cancer is the most common cancer among women, with a lifetime risk of up to 12% and a risk of death of up to 5%.[1] It is common for patients diagnosed with breast cancer to require multi-modality therapies that include surgery, radiotherapy, chemotherapy and hormonal therapy, separately or in combination, depending on the stage of cancer.[2] Radiotherapy is one of the major components of breast cancer treatment and is often used to prevent recurrence of breast cancer after breast-conserving surgery.[3] One of the dose-limiting effects of radiotherapy is the skin reaction that ionising radiation induces in normal tissue.[4] Radiotherapy treatment may cause mild to severe side effects such as erythema, desquamation, bullae/ulcers and skin necrosis,[5] which contribute to pain, discomfort, irritation, itching and burning.[6] Severe radiation skin changes may significantly interfere with the patient's daily activities and quality of life, affecting patient compliance and thereby reduce radiotherapy effectiveness, rendering it necessary to interrupt treatment.[5–7]

Many general interventions for the prevention and management of radiation skin reactions are reported in the literature and various formulations have been recommended. However, reported results are often conflicting.[6] Several studies have been conducted to evaluate the effectiveness of topical applications of corticosteroids,[8,9] hyaluronic acid,[4] sucralfate,[10] aloe vera,[11] dexpanthenol[12] and the use of barrier films or hydrophilic dressings.[13] In these studies, visual assessment by the Radiation Therapy Oncology Group (RTOG) acute toxicity scale is the clinical investigation method most commonly used to evaluate the frequency and the severity of skin reactions during and after radiotherapy.[14] When objective and quantitative

Correspondence: Prof. Carmelo Puglia, Department of Pharmaceutical Sciences, School of Pharmacy, University of Catania, Viale A Doria 6, 95125 Catania, Italy.
E-mail: capuglia@unict.it

data are required, additional non-invasive methods are preferred for more accurate evaluations of adverse skin effects. This can be achieved by non-invasive instrumental methods such as near-infrared spectroscopy,[15] laser Doppler perfusion imaging,[16] reflectance colorimetry,[17] reflectance spectrophotometry and digital photography.[18]

Since few studies have been carried out using a non-treated comparator group, it is difficult to support the success of topical treatments in the prevention or management of acute skin reactions.[6,9] In view of the limitations of earlier work, this study was conducted to evaluate the effects of protective topical agents as supportive care in the treatment of radiation-induced skin disease.

At present, Biafin (trolamine) is the most common topical agent used in preventing radiation-induced skin diseases. Several studies have failed to support a preference for the use of Biafin over the best supportive care or other topical agents.[7,19,20] However, Biafin is well-tolerated, and Fisher *et al*.[7] indicated that it was probably more effective in healing radiation-induced dermatitis than no treatment.

Furthermore, we have evaluated a topical agent composed of a blend of natural extracts containing polysaccharides of *Opuntia ficus indica* cladodes and biophenols of *Capparis spinosa* buds and *Olea europeae* leaves. The *Capparis spinosa* bud extract has been shown to possess in-vivo photoprotection activity against UVB-induced skin erythema[21] and in a recent study it was shown to counteract the harmful effects induced by pro-inflammatory mediators in human chondrocyte cultures.[22] Recent scientific evidence points to the effectiveness of olive polyphenols against skin UVB-induced inflammatory processes.[23] Moreover, olive polyphenolic bio-active compounds have been shown to possess antioxidant and free radical scavenging activity.[24,25] Finally, polysaccharides of *Opuntia ficus indica* cladode extract show a healing-accelerator and skin immunomodulatory activity that stimulates the skin regenerative physiological mechanisms.[26,27]

To assess the effectiveness of the topical agents Biafin and the blend of natural extracts, the study was conducted on subjects at risk of post-radiation skin reactions and for which a care regime for radiation-induced skin disease could be suggested. Moreover, in this study two different methods of measuring skin erythema resulting from radiation were compared: skin reactions were evaluated by an instrumental erythema index obtained from a non-invasive reflectance spectral method as well as from the RTOG visual scoring system.

Materials and Methods

Participant recruitment

The study was conducted on 68 volunteer women who were undergoing a planned course of radiation therapy after breast-conserving surgery, referred to the Department of Radiotherapy at Humanitas Centro Catanese di Oncologia. Each volunteer was fully informed of the nature of the study and of the procedures involved. Substances commonly used in the treatment of different skin diseases, with no harmful effects for the subjects, and non-invasive instrumental methods were used to measure the effects on the skin. Informed consent was required from all the participants in the study. Age, tumour stage, smoking status, skin type and breast size were recorded for each volunteer. Subjects receiving concomitant systemic anticancer treatment or prior radiation therapy, exhibiting cutaneous disease (rash, bleeding, ulceration or unhealed scar) or demonstrating allergy or sensitivity to the formulations were excluded.

Topical application of formulations

In this study, two topical formulations were used to treat radiotherapy-induced skin damage. Formulation A was an emulsion consisting of 3% w/w of a blend of natural extracts containing *Capparis spinosa*, *Opuntia coccinellifera* and olive leaf extracts (Skin Save; Bionap, Italy) and ingredients typically found in skin care products, as reported in Table 1. The O/W (oil in water) emulsion was prepared by slowly adding the aqueous phase to the oily phase and a blend of surfactants under continuous agitation; both phases were kept at 70°C. This mixture was stirred until it was cool, thus forming the emulsion formulation.

Formulation B was Biafin (Istituto Ganassini, Italy), a commercialised non-steroidal topical product. The formulation is a water-based emulsion, with the composition, as reported on the packaging, shown in Table 1.

Participants in the study were randomly allocated to receive one of the topical treatments (formulation A or formulation B) or no treatment (Table 2). Subjects allocated to use treatment A or B were instructed to apply a thin layer of cream twice daily to the treatment area from the first day of radiotherapy. The formulation was not applied within 4 h of the radiation session.

Assessment measures

Baseline skin assessment by RTOG visual score and reflectance spectrophotometry (X-Rite mod. 968, with 0° illumination and 45° viewing angle) was performed in all subjects. Reflectance

Table 1 Composition of formulation A (Skin Save) and formulation B (Biafin) evaluated in the treatments of radiation induced skin disease

Formulation A	
Oil phase	PPG-15 stearyl ether (8 g); isohexadecane/PPG-15 stearyl ether (4 g)
Aqueous phase	Distilled water (73.7 g); Skin Save (3 g)
Surfactants and structurising agents	Steareth 2 (3.5 g); steareth 21 (2.5 g); stearic acid (2.5 g); cetylstearylic acid (2.1 g); xanthan gum (0.3 g); ethylene glycolphenyl undecylether p-hydroxybenzoate (0.4 g)
Formulation B	
Aqua, paraffinum liquidum, glycol stearate, stearic acid, propylene glycol, paraffin, squalane, avocado oil, triethanolamine alginate and sodium salt, triethanolamine (total triethanolamine 0.7%), cetyl palmitate, parfum, potassium sorbate, sodium methylparaben, sodium propylparaben	

Table 2 Characteristics of subjects in formulation A (Skin Save), formulation B (Biafin) and no treatment groups

Characteristics	Formulation A (n = 26)	Formulation B (n = 24)	No treatment (n = 18)
Median age (range) (years)	48 (41–56)	52 (38–65)	50 (45–58)
Breast			
Right	8 (31%)	13 (54%)	6 (33%)
Left	18 (69%)	11 (46%)	12 (67%)
Tumour location			
Medial	8 (31%)	6 (25%)	7 (39%)
Lateral	14 (54%)	17 (71%)	11 (61%)
Central	4 (15%)	1 (4%)	0 (0%)
Skin phototype			
Type 1	0 (0%)	0 (0%)	0 (0%)
Type 2	12 (46%)	10 (42%)	10 (56%)
Type 3	14 (54%)	14 (58%)	8 (44%)
Type 4	0 (0%)	0 (0%)	0 (0%)
Use of tobacco			
Non-smoker	10 (38%)	8 (33%)	6 (33%)
Ex-smoker	5 (20%)	6 (25%)	5 (28%)
Current smoker	11 (42%)	10 (42%)	7 (39%)
Brassiere cup size			
Size A	0 (0%)	0 (0%)	0 (0%)
Size B	10 (38%)	10 (42%)	10 (56%)
Size C	14 (54%)	11 (46%)	8 (44%)
Size D	2 (8%)	3 (12%)	0 (0%)

spectra were obtained over the wavelength range 400–700 nm using illuminant C and 2° standard observer. The instrument has been used in previous studies to monitor and measure skin erythema.[28] To include the large skin area involved in the radiation treatment, the field for the assessment of erythema was divided into three regions (lateral breast, medial breast and under the breast) (Figure 1). For each skin region, reflectance spectra were recorded once a week, and the erythema index was calculated from these values as follows. Since erythema is due to an increment of blood count in the subpapillary plexus of the skin, erythema index (EI) values were calculated by subtracting the logarithm of inverse reflectance (log1/R) values at 510 nm and 610 nm (mainly due to melanin absorption) from the sum of haemoglobin (log1/R) values of 540, 560 and 580 nm, which represent the wavelengths of the haemoglobin absorption peaks (eqn 1).[28] All the regions were measured in triplicate.

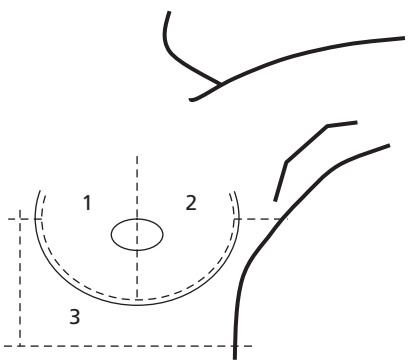

Figure 1 Regions of the breast for erythema assessment. (1) medial breast, (2) lateral breast and (3) under the breast

$$EI = 100\left[\log\frac{1}{R_{560}} + 1.5\left(\log\frac{1}{R_{540}} + \log\frac{1}{R_{580}}\right) - 2\left(\log\frac{1}{R_{510}} + \log\frac{1}{R_{610}}\right)\right] \quad (1)$$

The mean of the EI values obtained for all designated regions was defined as the subject EI. To evaluate the time-course of skin radiation-induced reactions, EI baseline values were subtracted from the EI values obtained from weekly subject inspection, to calculate ΔEI values. Plotting ΔEI vs time, the area under the response ΔEI–time curve of each subject was calculated using the trapezoidal rule to obtain the AUC (area under curve), giving dimensionless index values directly related to the degree of radiation-induced skin erythema. AUC values were calculated for the monitoring period of 8 weeks ($AUC_{1–8}$) and at different time intervals: from the first to the third week ($AUC_{1–3}$), from the fourth to the sixth week ($AUC_{4–6}$) and from the seventh to the eighth week ($AUC_{7–8}$).

Visual assessment with reference to erythema, oedema, desquamation and ulceration of each region was performed in each weekly inspection according to the modified RTOG scoring system proposed by Wells *et al.*[10] (Table 3), and photodocumentation of treated skin was performed for a subsequent verification of the RTOG visual score.

Statistical methods

The subjects admitted into the study were randomised into one of the three groups using a computer-generated randomisation list. Neither the research assistants nor the volunteers knew the content of the tubes containing formulation A or B. The code was broken after the last subject had completed her follow-up. All data obtained were submitted to a statistical analysis. All statistical comparisons were evaluated using Kruskal–Wallis tests and Dunn's post-hoc test.

Results

A total of 68 subjects were admitted into the study: 26 subjects were randomly allocated to use treatment A, 24 were in the B group and 18 subjects received no treatment. The average age of participants was 50, ranging from 38 to 65 years. Pre-treatment characteristics appear in Table 2. Skin reflectance spectra were recorded by reflectance spectrophotometry and the

Table 3 Modified Radiation Therapy Oncology Group scale for visual assessment of radiation-induced skin erythema

RTOG visual score	Skin changes
0	None
1	Follicular, faint or dull erythema
1.5	Dry desquamation
2	Tender or bright erythema
2.5	Patchy moist desquamation
3	Confluent moist desquamation
4	Ulceration, haemorrhage, necrosis

From Weels *et al.*[10]

EI was calculated for each subject. The trends in mean EI variation (ΔEI) vs time for subjects are reported in Figure 2. A significant increase in ΔEI was observed in the non-treated group after the second week of radiotherapy and maximal values were recorded between the fourth and sixth week. $AUC_{1–8}$ values of each subject calculated for 8 weeks and the group mean $AUC_{1–8}$ values are reported in Table 4 and Figure 3. The results show lower $AUC_{1–8}$ values in the A and B groups than in the non-treated group ($P < 0.01$). Formulation A was significantly more effective than B in preventing or reducing radiotherapy-induced skin reactions ($P < 0.05$). To compare the time course of erythema, AUC values for all subjects were calculated by spectral data at different time intervals ($AUC_{1–3}$, $AUC_{4–6}$ and $AUC_{7–8}$), as reported in Figure 3. In the first time interval ($AUC_{1–3}$), use of formulations A and B was associated with a statistically significant reduction in the degree of erythema ($P < 0.01$) compared with the non-treated group. However, no significant difference was found between these two formulations until the fourth week ($P > 0.05$). After the fourth week ($AUC_{4–6}$ and $AUC_{7–8}$), formulation A showed AUC values significantly lower than AUC values obtained from formulation B (Figure 3).

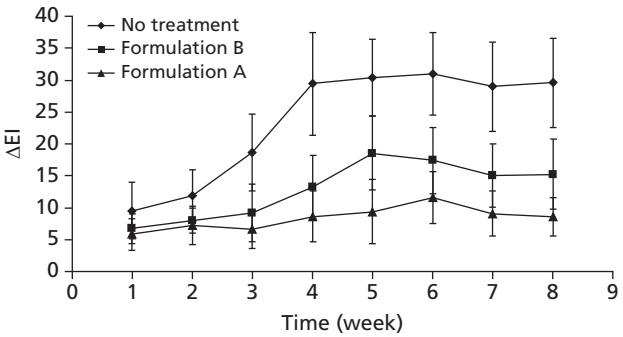

Figure 2 Trends of erythema index variation vs time

The correlation between the degree of radiation-induced skin reaction and tobacco use was also estimated in this study. We observed that subjects recruited in this study who had never smoked showed lower skin erythema than smokers and ex-smokers. However, statistical analysis of AUC values (Table 5) showed that there was no significant difference in skin erythema between the smokers and non-smokers allocated to each group (no treatment, formulation A and formulation B). We may suppose that the lack of association between smoking and skin reactions may be explained by the fairly small portion of non-smoker subjects recruited into each group.

Table 4 Treatment responses

No treatment			Formulation A			Formulation B		
Subject no.	$AUC_{1–8}$	RTOG visual score	Subject no.	$AUC_{1–8}$	RTOG visual score	Subject no.	$AUC_{1–8}$	RTOG visual score
1	90.58	2	**2**	65.21	2	**3**	48.74	1.5
4	138.09	4	**5**	72.87	2	**6**	57.15	2
7	217.33	3	**8**	33.37	1	**9**	72.12	2
10	137.69	3	**11**	87.04	2	**12**	155.38	4
13	96.57	3	**14**	50.10	2.5	**15**	128.14	2.5
16	85.74	1.5	**17**	45.21	3	**18**	78.79	2.5
19	207.58	4	**20**	41.87	3	**21**	54.23	3
22	256.04	3	**23**	50.23	2.5	**24**	58.12	3
25	137.38	3	**26**	48.75	2.5	**27**	71.84	2
28	216.37	4	**29**	73.01	2	**30**	47.20	2
31	89.65	2.5	**32**	49.99	2	**33**	139.39	2
34	250.74	4	**35**	43.61	1	**36**	118.32	2
37	216.40	3	**38**	102.32	2	**39**	81.35	2
40	123.81	3	**41**	51.08	2.5	**42**	74.87	3
43	253.70	4	**44**	128.02	2	**45**	108.16	2.5
46	267.90	4	**47**	56.99	1.5	**48**	54.27	2
49	190.00	4	**50**	79.23	2.5	**51**	98.63	2.5
52	70.35	2.5	**53**	39.00	2	**54**	115.68	2.5
			55	53.67	2	**56**	35.31	1.5
			57	47.33	2.5	**58**	76.37	2
			60	95.03	2	**61**	90.78	3
			62	60.38	1.5	**63**	117.34	2.5
			64	107.26	2.5	**65**	134.67	2.5
			66	43.90	1.5	**67**	147.36	3
			68	37.12	1			
			69	54.22	1.5			
Mean	**169.22**	**3.19**		**62.19**	**2.02**		**90.18**	**2.4**
± SD	**68.30**	**0.77**		**24.26**	**0.56**		**35.21**	**0.57**

Responses shown for each of the subjects admitted into the study, divided into the three groups: formulation A, formulation B, no treatment. AUC, area under the response ΔEI–time curve obtained from spectral data, values shown ± SD over the monitoring period of 8 weeks ($AUC_{1–8}$); RTOG, Radiation Therapy Oncology Group.

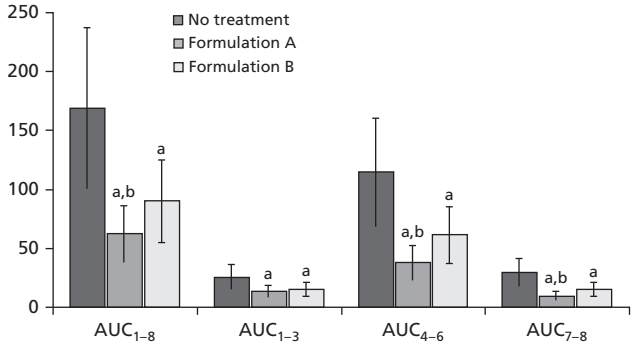

Figure 3 Mean area under curve value for different periods. AUC values (± SD) from subjects of formulation A (Skin Save), formulation B (Biafin) and the no treatment groups over the monitoring period of 8 weeks and at different time intervals (from the first to the third weeks $AUC_{1–3}$, from the fourth to the sixth weeks $AUC_{4–6}$ and from the seventh to the eighth week $AUC_{7–8}$); [a]significantly different ($P < 0.05$) compared to the non treated group; [b]significantly different ($P < 0.05$) compared to formulation B

Table 5 Comparison of smokers, ex-smokers and non-smokers

	No treatment	Formulation A	Formulation B
Non-smokers	115.01 ± 54.53	56.84 ± 22.99	76.71 ± 33.64
Ex-smokers + current smokers	196.32 ± 58.77[a]	65.53 ± 25.15[a]	96.91 ± 32.07[a]

Comparison between $AUC_{1–8}$ (area under the response ΔEI–time curve obtained from spectral data) values (± SD) in non-smokers and ex/current smokers; [a]not significantly different compared to non-smokers ($P > 0.05$).

The modified RTOG visual score system was also used to record radiotherapy-induced skin reactions. There were no differences in the RTOG visual score between subjects in the different groups at baseline and all subjects scored 0. In Table 4, the maximal assessed RTOG visual score for subjects in each group is reported over the 8-week observation period. As shown, an elevated percentage of subjects in the no-treatment group (78% for maximal score >2.5) developed severe erythema and desquamation in the irradiated skin area. Both formulations A and B were efficacious against the development of erythema in comparison with the non-treated group ($P < 0.01$). However, no significant difference ($P > 0.05$) was observed in the RTOG visual score system between formulation A and formulation B in reducing skin erythema induced by irradiation (Figure 4).

Discussion

Treatment with ionising radiation after breast-conserving surgery is used to prevent recurrence of breast cancer in women. The aim of radiotherapy is to destroy cancer cells, but radiation passing through the healthy skin causes severe damage to the cutaneous living layers and a variety of skin reactions occur that may interfere with patient quality of life and affect patient compliance with radiotherapy.

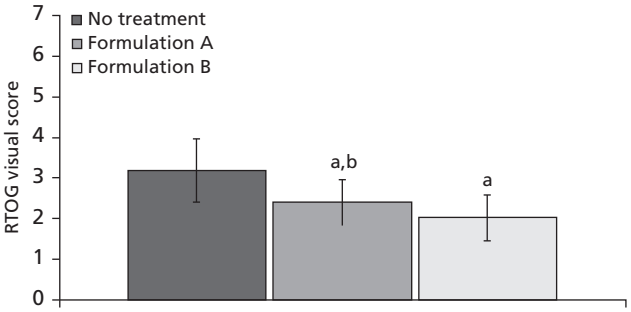

Figure 4 RTOG visual scores. Scores shown for subjects of formulation A (Skin Save), formulation B (Biafin) and the no treatment group; [a]significantly different ($P < 0.01$) compared to the non-treated group; [b]not significantly different ($P > 0.05$) compared to formulation B

Instructions for skin care during radiation therapy include washing the treated skin area with mild soap or cleansing agents, and avoiding chemical irritants, damage from abrasion or extremes of temperature. In addition, there are a variety of treatment procedures recommended for the management of radiation skin reactions using topical products. However evidence to support the benefit obtained by applying these topical agents to the treated area is lacking.

In the present study we investigated the ability of the topical agents Biafin and a blend of herbal extracts (*Capparis spinosa*, *Opuntia coccinellifera* and olive leaf extracts) to minimise radiation-induced skin disease in comparison with a non-treated group.

From the results obtained we observed, using spectrophotometric evaluation of radiotherapy-induced skin erythema, that there was an increase of skin reactions in the non-treated group after the second week of the monitoring period and maximal alterations between the fourth and sixth week. The primary response of the radiation insult to the skin may be the production of substances (such as IL-1, TNF, histamine, nitric oxide, etc.) from epithelial cells, endothelial cells and mast cells, which are known to promote vasodilatation and induce increased blood volume beneath the epidermis. In this phase it is very difficult to evaluate and quantify the skin erythema by visual assessment, and a sensitive instrumental method was required.[16] Recently, several studies evaluated radiotherapy-induced skin erythema by reflectance spectrophotometry.[5,10,18] In these reports, the degree of erythema was measured by a narrow-band reflectance spectrophotometer emitting a selected light wavelength of 568 nm, corresponding to the absorption peak of haemoglobin, the main chromophore in the dermal vasculature. The intensity of light reflected was detected and computerised, yielding an EI value. However, since none of the main skin chromopheres (haemoglobin and melanin) absorb in narrow bands, the obtained EI is not exclusively a linear function of haemoglobin content, but is affected by skin melanin content.[29] In this study, the EI calculated from skin reflectance spectra provides a more accurate and reliable evaluation of skin haemoglobin quantity because spectral values permit the EI to be calculated by subtracting the main melanin absorption peaks (510 and 610 nm) from the haemoglobin absorption peaks at wavelengths of 540, 560 and 580 nm.[28]

Using this sensitive reflectance spectrophotometric approach, we were able to demonstrate an important reduction in early erythema by application of topical agents. In fact, both tested formulations were able to reduce the transient erythema induced by radiation treatment in comparison with the non-treated group.

After the third to fourth week, examination of the erythema time-course showed an increase in the degree of erythema in untreated subjects. Dryness and moist desquamation could be visibly localised to the treated field at the end of the monitoring period. At this stage of radiation treatment, additional inflammatory mediators are released secondary to the necrosis of epithelial cells killed by radiation and there is a decrease in the ability of the basal layer to replace surface layers.[6,16]

In contrast to several studies reported in the literature,[7,8,19] our results suggest that topical therapies can significantly reduce skin reactions induced by radiation. One reason for the discrepant findings may be that these previous studies used a less sensitive tool to evaluate skin erythema, compared to the instrumental tool used here. Visual assessment of the actual degree of erythema developing during radiotherapy may have been impaired by a concomitant increase in melanin levels in the treated skin.[18] Spectrophotometric reflectance spectra and calculated ΔEI and AUC values used to quantify erythema in radio-induced skin reactions may avoid the shortcomings in visual assessment through their ability to grade slight differences in levels of erythema.

It is possible to suppose that Biafin (trolamine) and the herbal extracts may affect the mechanisms involved in radiation-induced skin erythema. As reported in the literature,[7,20] Biafin can enhance skin healing by recruiting macrophages and modifying the concentration of various immunomodulators.

The involvement of free radical overproduction during radiation treatment can explain the beneficial effects obtained by the topical application of *Capparis spinosa*, *Olea europeae* and *Opuntia ficus indica* extracts. The killing action of radiation is mainly caused by the production of free radicals by the radiolytic decomposition of cellular water. The free radical overproduction results in an imbalance of pro-oxidants and antioxidants (oxidative stress) and leads to cell death. The response of normal tissues to the oxidative stress induced by radiation mainly depends on the ability of cells to maintain optimal function in response to free radical-induced damage at the biochemical level.[30,31] The blend of *Capparis spinosa*, *Olea europeae* and *Opuntia ficus indica* extracts is characterised by polyphenolic and polysaccharidic biologically active compounds. Polyphenols, such as flavonoides, secoiridoides and hydroxycinnamic acid, contained in the blend of extracts can exert a considerable protective effect against oxidative stress induced by free radicals.[21–25] Furthermore, polysaccharidic actives are able to affect the physiological skin mechanisms that counteract skin degenerative events in wound-healing events, accelerating the natural reparatory process.[26,27]

Conclusions

The results obtained in this study have highlighted the benefit that can be obtained by topical therapy for skin receiving radiation treatment. Biafin (trolamine) and a blend of herbal extracts can be useful in the prevention and management of skin reactions induced by radiotherapy. The blend of herbal extracts containing *Capparis spinosa*, *Opuntia coccinellifera* and olive leaf extracts was significantly more effective than Biafin in preventing acute skin reactions. The topical therapies showed no harmful effects and could be used to promote comfort in subjects receiving radiation treatment as supportive care of skin reactions.

Moreover, the instrumental approach by reflectance spectrophotometry used in this study should avoid the shortcomings in visual assessment through its ability to grade slight differences in levels of erythema and it should facilitate the evaluation of the effectiveness and activity of topical agents in all the phases of radiotherapy-induced skin reactions.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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References

1. Soerjomataram I *et al*. An overview of prognostic factors for long-term survivors of breast cancer. *Breast Cancer Res Treat* 2008; 107: 309–330.
2. Shafiq J *et al*. An evidence-based estimation of local control and survival benefit of radiotherapy for breast cancer. *Radiother Oncol* 2007; 84: 11–17.
3. Bartelink H *et al*. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001; 345: 1378–1387.
4. Liguori V *et al*. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. *Radiother Oncol* 1997; 42: 155–161.
5. Bostrom A *et al*. Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study. *Radiother Oncol* 2001; 59: 257–265.
6. McQuestion M. Evidence-based skin care management in radiation therapy. *Semin Oncol Nurs* 2006; 22: 163–173.
7. Fisher J *et al*. Randomized phase III study comparing best supportive care to Biafin 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.
8. Schmuth M *et al*. Topical corticosteroid therapy for acute radiation dermatitis: a prospective randomized, double-blind study. *Br J Dermatol* 2002; 146: 983–991.
9. Bolderston A *et al*. The prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. *Support Care Cancer* 2006; 14: 802–817.
10. Wells M *et al*. Does aqueous or sucralfate cream affect the severity of erythematous radiation skin reactions? A randomised controlled trial. *Radiother Oncol* 2004; 73: 153–162.

11. Williams MS *et al*. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys* 1996; 36: 345–349.
12. Röper B *et al*. Thêta-Cream® versus Bepanthol® lotion in breast cancer patients under radiotherapy. *Strahlentherapie und Onkologie* 2004; 180: 315–322.
13. Graham P *et al*. Randomized, paired comparison of no-sting barrier film versus sorbolene cream (10% glycerine) skin care during postmastectomy irradiation. *Int J Radiat Oncol Biol Phys* 2004; 58: 241–246.
14. Lopez E *et al*. Breast cancer acute radiotherapy morbidity evaluated by different scoring systems. *Breast Cancer Res Treat* 2002; 73: 127–134.
15. Nyström J *et al*. Objective measurement of radiotherapy-induced erythema. *Skin Res Technol* 2004; 10: 242–250.
16. Simonen P *et al*. Do inflammatory processes contribute to radiation induced erythema observed in the skin of humans? *Radiother Oncol* 1998; 46: 73–82.
17. Pièrard GE. EEMCO guidance for the assessment of skin colour. *J Eur Acad Dermatol Venereol* 1998; 10: 1–11.
18. Wengström Y *et al*. Quantitative assessment of the skin erythema due to radiotherapy-evaluation of different measurements. *Radiother Oncol* 2004; 72: 191–197.
19. Fenig E *et al*. Topical Biafine and Lipiderm for the prevention of radiation dermatitis: a randomized prospective trial. *Oncol Rep* 2001; 8: 305–309.
20. Pommier P *et al*. Phase III randomized trial of *Calendula officinalis* compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. *J Clin Oncol* 2004; 15: 1447–1454.
21. Bonina F *et al*. In vitro and in vivo photoprotective effects of a lyophilized extract of *Capparis spinosa* L. buds. *J Cosmet Science* 2002; 53: 321–335.
22. Panico AM *et al*. Protective effect of *Capparis spinosa* on chondrocytes. *Life Sci* 2005; 77: 2479–2488.
23. Perugini P *et al*. Efficacy of oleuropein against UVB irradiation: preliminary evaluation. *Int J Cosmet Sci* 2008; 30: 113–120.
24. De Leonardis A *et al*. Isolation of a hydroxyltyrosol-rich extract from olive leaves (*Olea Europeae* L.) and evaluation of its antioxidant properties and bioactivity. *Eur Food Res Technol* 2008; 226: 653–659.
25. Saija A *et al*. In vitro evaluation of the antioxidant activity and biomembrane interaction of the plant phenols oleuropein and hydroxytyrosol. *Int J Pharm* 1998; 166: 123–133.
26. Trombetta D *et al*. Effect of polysaccharides from *Opuntia ficus-indica* (l.) cladodes on the healing of dermal wounds in the rat. *Phytomedicine* 2006; 13: 352–358.
27. Park E-H, Chun M-J. Wound healing activity of *Opuntia ficus-indica*. *Fitoterapia* 2001; 72: 165–167.
28. Puglia C *et al*. Evaluation of in vivo topical anti-inflammatory activity of indometacin from liposomal vesicles. *J Pharm Pharmacol* 2004; 56: 1225–1232.
29. Suh DH *et al*. Changes of skin blood flow and color on lesional and control sites during PUVA therapy for psoriasis. *J Am Acad Dermatol* 2001; 44: 987–994.
30. Cetin A *et al*. The effect of grape seed extract on radiation-induced oxidative stress in the rat liver. *Turk J Gastroenterol* 2008; 19: 92–98.
31. Crohns M *et al*. Local and systemic oxidant/antioxidant status before and during lung cancer radiotherapy. *Free Radic Res* 2009; 43: 646–657.