Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature

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ABSTRACT

Radiation therapy is a common treatment for cancer patients. One of the most common side effects of radiation is acute skin reaction (radiation dermatitis) that ranges from a mild rash to severe ulceration. Approximately 85% of patients treated with radiation therapy will experience a moderate-to-severe skin reaction. Acute radiation-induced skin reactions often lead to itching and pain, delays in treatment, and diminished aesthetic appearance—and subsequently to a decrease in quality of life.

Surveys have demonstrated that a wide variety of topical, oral, and intravenous agents are used to prevent or to treat radiation-induced skin reactions. We conducted a literature review to identify trials that investigated products for the prophylaxis and management of acute radiation dermatitis. Thirty-nine studies met the pre-defined criteria, with thirty-three being categorized as prophylactic trials and six as management trials.

For objective evaluation of skin reactions, the Radiation Therapy Oncology Group criteria and the U.S. National Cancer Institute Common Toxicity Criteria were the most commonly used tools (65% of the studies). Topical corticosteroid agents were found to significantly reduce the severity of skin reactions; however, the trials of corticosteroids evaluated various agents, and no clear indication about a preferred corticosteroid has emerged. Amifostine and oral enzymes were somewhat effective in preventing radiation-induced skin reactions in phase II and phase III trials respectively; further large randomized controlled trials should be undertaken to better investigate those products. Biafine cream (Ortho–McNeil Pharmaceuticals, Titusville, NJ, U.S.A.) was found not to be superior to standard regimes in the prevention of radiation-induced skin reactions ($n = 6$).

In conclusion, the evidence is insufficient to support the use of a particular agent for the prevention and management of acute radiation-induced skin reactions. Future trials should focus on comparing agents and approaches that, in phase I and II trials, suggest efficacy. These future phase III randomized controlled trials must clearly distinguish between preventive and management strategies for radiation-induced dermatitis. Only then can evidence-based guidelines be developed, with the hope of standardizing the approach across centres and of improving the prevention and management of radiation-induced dermatitis.

KEY WORDS

Radiation dermatitis, radiotherapy, review, skin reaction

1. INTRODUCTION

The goal of radiotherapy is to provide maximum benefit to the patient with minimal side effects [1]. However, even with the most modern radiotherapy techniques, up to 90% of patients will experience a dose-dependent skin reaction at the treated area [1–4]. Skin reactions related to radiation therapy usually manifest within 1–4 weeks of radiation start, persist for the duration of radiation therapy, and may require 2–4 weeks to heal after completion of therapy [5]. The severity of the skin reaction ranges from mild erythema (red rash) and dry desquamation (itchy, peeling skin) to more severe moist desquamation (open wound) and ulceration [6].

After the initial dose of radiation, tissue damage occurs immediately, and every subsequent fraction of radiation generates inflammatory cell recruitment. Acute radiation dermatitis is the combined result of a decrease in functional stem cells, changes in the skin's endothelial cells, inflammation, and skin-cell necrosis and death [7]. Potential complications of radiation dermatitis in the acute setting include local infection. The severity of the reaction is related to the dose per fraction, total dose delivered, use of bolus or other

beam-modifying devices, size of the treatment field, site treated, use of concurrent chemotherapy or other agents, and individual susceptibility [8]. Areas of the body that contain skin folds, such as the groin, are at higher risk of developing a reaction because of a phenomenon called the "bolus effect"; these areas are more likely to receive a higher dose of radiation and more prone to bacterial contamination [9]. Prescribed treatment at low doses (<2000 cGy) in conventional fractionation at depth usually does not elicit a skin reaction, and consequently, patients receiving palliative treatment are not usually at risk [6].

Prevention and management of radiation-induced skin reactions are often confusing processes for patient and clinician alike. A study conducted in the United Kingdom noted substantial variation in the advice given to patients by different radiotherapy departments (n = 33) for preventing and managing skin reactions [10]. A survey of nursing practice in Belgium revealed that management of skin reactions varies, and traditional practices such as avoiding skin washing and using talcum powder are still advised by a significant number of nurses even though those practices are controversial in the literature [11]. The high incidence of radiation-induced skin reactions has generated interest in methods of preventing and effectively treating such reactions [1].

It is generally agreed that the ideal method for preventing and minimizing skin reactions is moisturization of the irradiated area. The use of barrier or corticosteroid creams, *Aloe vera*, and other lanolin-free hydrophilic products is often recommended for this purpose [1]. A Cancer Care Ontario guideline for the prevention of skin reactions suggests skin washing with mild soap and water, but because of limited evidence, suggests no specific products for prevention or management [6]. The objective of treatment for dry desquamation is to lessen patient discomfort by providing moisture to the affected areas [12]. Treatment of moist desquamation usually involves the use of hydrocolloid dressings to reduce exposure to external pathogens and ultimately to prevent infection [1]. Although a general consensus among radiotherapy centres is lacking, the advice given to patients has a few commonalities:

- During or after radiation treatment, avoid the use of metallic-based topical products (zinc oxide creams or deodorants with an aluminum base, for instance), because they may increase the surface dose to skin [12].
- Wear loose-fitting clothing over the irradiated area to prevent friction injuries [1,12].
- Maintain a clean and dry irradiated area [1].
- Avoid extreme temperatures [1].
- Avoid the use of starch-based products because they increase the risk of infection [1].

No general accord has been reached across radiotherapy centres about the treatment of radiation skin toxicities. An updated review summarizing comparative studies that have evaluated the use of agents for the prevention and management of radiation-induced skin reactions is therefore needed, because additional studies in the literature may lead to consensus.

2. MATERIALS AND METHODS

We used the earlier Cancer Care Ontario publication from the Program in Evidence-Based Care [6] as a template. Our goal was to update the literature search and to use the earlier reporting structure to facilitate comparisons. We searched the MEDLINE, PubMed, and Cochrane Library databases to uncover comparative studies published between January 1, 2000, and October 1, 2008, thus updating the previous systematic review of the literature [6], which included studies up to April 2004. To find relevant articles, we used the search terms "dermis," "skin reactions," "radiation," "radiation adverse effects," "erythema," "desquamation," "radiodermatitis," "acute," and "radiotherapy adverse effects." Searches were limited to the English language, to studies conducted on human subjects, and to publications of randomized controlled trials (RCTS), controlled clinical trials, and comparative studies. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from those sources, and from review articles, were searched for additional trials.

2.1 Eligibility Criteria

Articles were included if they were fully published reports or published abstracts of clinical trials or studies that compared practices for the prevention or management of acute radiation-induced skin reactions and were published between January 1, 2000, and October 1, 2008. To be included, the trials must have reported a method of grading for the skin reaction and must have statistically evaluated the skin reaction as a primary or secondary outcome. Other primary or secondary outcomes that were assessed included pain, itchiness, burning, quality of life, toxicities, and patient perspective of the product, agent, or technique. Prospective and retrospective data were included. Trials that involved radiation-induced reactions in mucosal areas only were not included in the review. Letters, comments, editorials, practice guidelines, case reports, systematic reviews, and meta-analyses were excluded.

This update was planned as a qualitative review of the literature; no meta-analysis or pooling of results was performed.

3. RESULTS

Three of the identified trials were excluded because of ineligibility. Two trials did not report a statistical evaluation of the agent; instead, they provided

subjective observation only [13,14]. The third trial had only an abstract in English translation, which did not allow for appropriate interpretation of results [15].

Thirty-nine trials met the inclusion criteria [2,3,16–52]. Thirty-three of those trials were aimed at preventing radiation-induced skin reactions [2,3,16–46], and six trials evaluated management regimens for existing skin reactions [47–52]. The agents evaluated in the trials varied greatly. Tables I–III outline the trial details, including trial type, treatment regimen, tumour site group, and results.

Twenty-six of the preventive trials were RCTs [2,16–25,27–32,34–37,41–44,46], six were nonrandomized clinical trials [3,26,33,38,39,45], and one was a retrospective trial [40]. Twenty-one of the trials were open [3,16,19,20,24–26,28,29,32–35,37–43,45], three were single-blind [17,22,27], and nine were double-blind [2,18,21,23,30,31,36,44,46]. Of the six management trials, three were RCTs [49,50,52], and three were nonrandomized clinical trials [47,48,51]. One of the trials was double-blind [52]; the remaining trials were open [47–49,51,52].

The data gathered for six of the included trials were limited because only abstracts were available [22,25,29,37,40,52]. Of the thirty-three studies from which additional information was gathered, six trials analyzed patients by intention to treat [16,17,30,32,35,50], and twenty-seven assessed only evaluable patients [2,3,18–21,23,24,26–28,31,33,34,36,38–44,46–49,51]. Reasons for exclusion of patients from analysis included lack of compliance with the agent or dressing, withdrawal from the study, or failure to show up to clinic appointments. Skin reactions were often assessed by one evaluator, which was commonly a radiation oncologist, dermatologist, research nurse, research assistant, radiation therapist, principal investigator, or other medical professional [3,17,20,21,24,26,27,32,33,35,39,44,46,50]. A few studies incorporated an inter-rater reliability measure by having more than one evaluator assess the skin reactions [23,34,36,45,49,51]; the remaining studies did not describe who assessed the radiated area or areas [2,16,19,25,28,30,31,38,41–43,47,48].

Additionally, among the thirty-three studies in which additional information was provided, seventeen used the Radiation Therapy Oncology Group (RTOG) radiation skin-toxicity grading tool (or a slightly modified version of it) [16,17,21,24,27,32–36,41,42,44,45,47,48,50]. The second most common tool in use was the U.S. National Cancer Institute's Common Toxicity Criteria (NCI CTC), which is similar to the RTOG and was used in nine studies [2,3,26,28,30,37–39,46]. The remaining studies used a study-designed tool closely modeled after either the RTOG or NCI tool, with slight variations [18–20,23,31,43,49].

3.1 Outcomes: Preventive Trials

3.1.1 Washing Practice

Two studies evaluated washing practice for preventing radiation dermatitis [16,17].

Roy *et al.* compared no washing with gentle washing using water and mild soap (Dove: Unilever Canada, Saint John, NB; Ivory: Procter and Gamble, Toronto, ON) during radiation for breast cancer. Compared with patients in the non-washing group, those in the washing group had a significantly lower incidence of moist desquamation ($p = 0.03$); however, patients did not differ on other parameters such as maximum erythema score and mean time to maximal toxicity. The variety of soaps used in the washing group was large, and washing routines were not identical across all patients in the group [17].

Westbury *et al.* looked at scalp care after cranial irradiation. Patients were randomized either to continue their normal hair-washing regime or to avoid washing the treatment area. The study did not find a significant difference in skin reactions between the two groups and did not report differences in pain or itchiness [16].

3.1.2 Topical Corticosteroid Agents

Four trials evaluated topical corticosteroids for the prevention of acute skin reactions [18–21].

Boström *et al.* [18] studied breast cancer patients receiving radiation after breast-conserving surgery. The patients received prophylaxis with either 0.1% mometasone furoate cream or an emollient cream in a blinded manner. Boström *et al.* found a significant benefit in favour of the mometasone furoate cream in maximum erythema scores ($p = 0.011$) and in grade 4 or greater (on a 7-point grading scale) skin reaction (25% vs. 60%).

In a randomized double-blind study, Schmuth *et al.* compared two topical corticosteroid agents: 0.5% dexpanthenol cream and 0.1% methylprednisolone aceponate cream [19]. These authors found that although neither cream reduced the incidence of radiation dermatitis, fewer patients in the methylprednisolone group developed a reaction with a score of 4 or more ($p < 0.05$) on a rating scale that summed the scores for erythema, desquamation, erosion, induration, or hyperpigmentation (each assessed on a 4-point Likert scale: 0, none; 1, mild; 2, moderate; 3, severe—maximum possible score, 15). No other significant differences were found between the two treatment groups with respect to other measures of efficacy.

Shukla *et al.* [20] evaluated beclomethasone dipropionate spray, comparing treated patients with a control group that did not use a topical agent on the irradiated area. Those authors noted a significant difference in the incidence of moist desquamation in favour of the topical corticosteroid spray (13% vs. 37%, $p = 0.0369$).

Omidvari and colleagues [21] also assessed betamethasone in comparison with a group using petrolatum-based emollient and with a control group. Compared with the petrolatum and control groups, the betamethasone group showed a favourable significant difference at week 3 in the number of patients that reached a grade 1 (RTOG) skin reaction ($p = 0.027$). Throughout

TABLE I Prevention of radiation skin reactions

Reference	*Study type*	*Blinding*	*Pts (n)*	*Treatment arms*	*Outcomes assessed*		
					Skin reaction	*Pain*	*Itching*
Washing practice							
Westbury *et al.*, 2000 [16]	RCT	None	55 54	Normal hair care (washing) Avoid hair washing	No significant differences	NA	NA
Roy *et al.*, 2001 [17]	RCT	Single	49 50	No washing during RT Washing with soap and water	Significant difference in incidence of moist desquamation (p=0.03) in favour of washing	No significant difference	No significant difference
Topical steroidal agents							
Boström *et al.*, 2001 [18]	RCT	Double	24 25	MMF cream Emollient cream (control)	MMF cream significantly reduced acute RD (p=0.0033)	No significant difference	No significant difference
Schmuth *et al.*, 2002 [19]	RCT	None	12 11 15	0.1% MPA cream 0.5% Dexpanthenol Untreated controls	Fewer patients with severity ≥4 in MPA group than in dexpanthenol group (p<0.05)	NA	No significant difference
Shukla *et al.*, 2006 [20]	RCT	None	30 30	Beclomethasone dipropionate spray Control (no spray)	Significant decrease in incidence of moist desquamation (p=0.0369) in favour of the spray	NA	NA
Omidvari *et al.*, 2007 [21]	RCT	Double	19 17 15	0.1% Betamethasone Petrolatum Control (no treatment)	Compared with the other groups, the betamethasone patients had less severe RD at the end of the third week (p=0.027)	NA	NA
Topical nonsteroidal creams—Aloe vera							
Olsen *et al.*, 2001 [22]	RCT	Single		Mild soap plus *Aloe vera* Mild soap (control)	No significant differences noted (protective effect noted in higher cumulative doses)	NA	No significant Difference
Heggie *et al.*, 2002 [23]	RCT	Double	107 101	*Aloe vera* cream Aqueous cream	Aqueous cream significantly better (p<0.001) at reducing dry desquamation	Aqueous cream significantly better (p=0.03) at reducing pain	Cumulative probability greater in *Aloe vera* arm (p<0.05)

TABLE I *(Continued)*

Reference	*Study type*	*Blinding*	*Pts (n)*	*Treatment arms*	*Outcomes assessed*		
					Skin reaction	*Pain*	*Itching*
Topical nonsteroidal creams—Biafine[a] (trolamine salicylate) cream							
Fisher *et al.,* 2000 [24]	Multicentre RCT	None	83 89	Biafine cream Best supportive care (control)	No overall difference for maximum dermatitis; no difference for prevention, time to, or duration of RD	NA	NA
Fenig *et al.,* 2001 [25]	RCT	None	74 in total	Biafine cream Lipiderm[b] cream No cream (controls)	No significant differences	NA	NA
Szumacher *et al.,* 2001 [26]	Nonrandomized trial	None	60	Biafine cream	Breast skin assessment questionnaire, scored according to NCIC (<grade 2, 15%; grade 2, 83%; grade 3, 2%; grade 4, 0%)	Frequency data collected, no significant data recorded	Frequency data collected, no significant data recorded
Pommier *et al.,* 2004 [27]	RCT	Single	126 128	Calendula ointment Biafine cream	Incidence of grade 2 or higher RD significantly lower (p<001) in favour of calendula	Average maximum pain lower (p=0.03) in favour of calendula	NA
Elliot *et al.,* 2006 [28]	Multicentre RCT	None	166 175 165	Prophylactic trolamine Interventional trolamine Institutional preference (control)	No significant differences	NA	NA
Ribet *et al.,* 2008 [29]	RCT	None	35 34	Avène[c] thermal spring water anti-burning gel Trolamine cream	No significant differences	NA	NA
Topical nonsteroidal creams—hyaluronidase-based							
Primavera *et al.,* 2006 [2]	RCT	Double	20	Xclair[d] on one area of irradiated skin and vehicle control on another area of irradiated skin	Xclair-treated areas were significantly better (p=0.031) at visit 5 only	No statistically significant difference	No statistically significant difference
Leonardi *et al.,* 2008 [30]	RCT	Double	22 18	Xclair Vehicle control	Statistically significant difference for maximum skin severity (p<0.0001) in favour of Xclair	No significant difference	No significant difference

TABLE I *(Continued)*

Reference	*Study type*	*Blinding*	*Pts (n)*	*Treatment arms*	*Outcomes assessed*		
					Skin reaction	*Pain*	*Itching*
Topical nonsteroidal creams—sucralfate or sucralfate derivatives							
Evensen *et al.*, 2001 [31]	RCT	Double	60	Na sucrose octasulfate and vehicle control (each on one side of the radiation field)	No significant differences	NA	NA
Wells M *et al.*, 2004 [32]	RCT	None	117 120 120	Aqueous cream Sucralfate cream No cream	No significant difference	No significant difference	No significant difference
Topical nonsteroidal creams—miscellaneous creams							
Momm *et al.*, 2003 [33]	Nonrandomized	None	63 25	Moist skin care with 3% urea lotion Control group treated with dry skin care	Significantly more patients in control group experienced grade 3 reactions (p=0.0007)	NA	NA
Röper *et al.*, 2003 [34]	RCT	None	10 10	Thêta-Cream[e] Bepanthol[f]	No significant differences	No significant difference	NA
Graham *et al.*, 2004 [35]	RCT	None	61	Half with Cavilon No Sting Barrier Film[g]; half with sorbolene cream	Lower skin toxicity in Cavilon No Sting group (p=0.005)	No significant difference	NA
Enomoto *et al.*, 2005 [36]	RCT	Double	15 15	RayGel[h] Placebo	Lower average skin grade score (123 vs. 93.7, statistically nonsignificant)	NA	NA
Ma *et al.*, 2007 [37]	RCT	None	75 51 54 38	No reaction: *lian bai* liquid No reaction: controls Grade 3 reaction: *lian bai* liquid Grade 3 reaction: controls	Lower incidence of skin reaction in *lian bai* group (p<0.01); wound healing time shorter in *lian bai* group (p<0.01)	NA	NA
Matceyevsky *et al.*, 2007 [38]	Clinical trial	None	24 30	Solaris lotion[i] Control	No significant differences for severity; significantly fewer treatment breaks for treatment arm (p=0.034)	NA	NA

TABLE I *(Continued)*

Reference	*Study type*	*Blinding*	*Pts (n)*	*Treatment arms*	*Outcomes assessed*		
					Skin reaction	*Pain*	*Itching*
Systemic interventions—amifostine							
Dunst *et al.*, 2000 [39]	Nonrandomized controlled trial	None	15	Radiochemotherapy with amifostine	Lower incidence of grade 2 skin reaction (p=0.009) in favour of amifostine group	NA	NA
			15	Radiochemotherapy without amifostine			
Kouvaris *et al.*, 2002 [40]	Retrospective	None	100	Cytoprotective treatment with intravenous infusion of amifostine	Reduced severity of dermatitis (p<0.001) in favour of the amifostine group	NA	NA
			120	Historical controls			
Systemic interventions—oral enzymes							
Dale *et al.*, 2001 [41]	RCT	None	60	Wobe–Mugos enzyme	Maximum extent of acute reactions reduced (p<0.001) in enzyme group	NA	NA
			60	No treatment			
Gurjal *et al.*, 2001 [42]	RCT	None	53	Wobe–Mugos enzyme	Severity significantly less (p<0.001) in enzyme-treated patients	No significant difference	No significant difference
			47	No treatment (control)			
Systemic interventions—pentoxyfylline							
Aygenc *et al.*, 2003 [43]	RCT	None	40	Pentoxifylline	No significant difference for acute skin reactions; p<0.05 in favour of pentoxifylline group for late skin changes	No positive effects found	NA
			38	Control			
Systemic interventions—supplements							
Lin *et al.*, 2006 [44]	RCT	Double	49	Pro-Z[j] (zinc) supplement	Grade 2 dermatitis (p=0.014) and grade 3 dermatitis (p=0.0092) earlier for placebo	NA	NA
			48	Placebo			
Dressings							
Vuong *et al.*, 2004 [45]	Clinical trial	None	15	Silver-leaf nylon dressing	Reduction of RD (p<0.0001) in favour of silver-leaf nylon dressing	NA	NA
			15	Historical controls			

TABLE I *(Continued)*

Reference	*Study type*	*Blinding*	*Pts (n)*	*Treatment arms*	*Outcomes assessed*		
					Skin reaction	*Pain*	*Itching*
Mode of radiation delivery							
DeLand *et al.,* 2007 [3]	Clinical trial	None	19 28	LED-treated IMRT-treated	Grade of skin reaction was significantly lower ($p<0.0001$) **with LED**	NA	NA
Pignol *et al.,* 2008 [46]	RCT	Double	169 173	Standard breast RT treatment Breast IMRT treatment	$p=0.002$ for incidence of moist desquamation in favour of IMRT	NA (presence of moist desquamation correlated with increased pain)	NA

[a] Ortho-McNeil Pharmaceuticals, Titusville, NJ, U.S.A.
[b] G-Pharm Limited, Salisbury, U.K.
[c] Pierre Fabre Dermo Cosmétique USA, Parsippany, NJ, U.S.A.
[d] Align Pharmaceuticals, Berkeley Heights, NJ, U.S.A.
[e] TheraCosm, Dellstedt, Germany.
[f] Bayer Schering Pharma AG, Wilmington, DE, U.S.A.
[g] 3M, St. Paul, MN, U.S.A.
[h] Reduced glutathione and anthocyanins (Healogica, New York, NY, U.S.A.).
[i] Eugene–Perma, Paris, France.
[j] Banner Pharmacaps, High Point, NC, U.S.A.
Pts = patients; RCT = randomized controlled trial; NA = not available; RT = radiation therapy; MMF = mometasone furoate; RD = radiation dermatitis; MPA = methylprednisolone aceponate; NCIC = National Cancer Institute of Canada; LED = light-emitting diode; IMRT = intensity-modulated radiotherapy.

TABLE II Management of radiation skin reactions

Reference	*Study type*	*Blinding*	*Pts (n)*	*Treatment arms*	*Outcomes assessed*		
					Skin reaction	*Pain*	*Itching*
Topical colony-stimulating factors							
Kourvaris *et al.,* 2001 [47]	Nonrandomized	None	37	Steroid cream on irradiated areas	Score of skin reactions ($p = 0.008$) in favour of GM-CSF gauze addition; healing time ($p = 0.02$) also significant	Pain grading ($p = 0.014$) in favour of gauze group	NA
			24	Steroid cream plus gauze impregnated with GM-CSF			
Topical nonsteroidal cream							
Garcia *et al.,* 2007 [48]	Phase I trial	None	57	Superoxide dismutase topical treatment	All patients had grade 2 toxicity to begin with, and 77.1% had at least a partial response at the end of RT; no worsening was seen at 12-weeks	NA	NA
Dressings							
Mak *et al.,* 2000 [49]	RCT		21	Moist hydrocolloid dressing	No significant differences	Severity and frequency significantly lower ($p = 0.012$ and $p = 0.03$ respectively) in favour of gentian violet	NA
			18	Topical gentian violet (control)			
Macmillian *et al.,* 2007 [50]	RCT	None	29	Simple dry dressing (control)	Healing times prolonged with the use of hydrogel (HR: 0.64: 95% CI: 0.42 to 0.99)	No statistically significant difference	No statistically significant difference
			54	Hydrogel plus Tricotex[a] as a secondary dressing			
Vavassis *et al.,* 2008 [51]	Clinical trial	None	12	Silver-leaf dressing on one side of neck; silver sulfadiazine on other side of neck	Reduction in severity of reaction within the same grade ($p = 0.035$) in favour of silver-leaf dressing	Subjectively superior for silver-leaf dressing in 67% of patients	NA
Other							
Balzarini *et al.,* 2000 [52]	RCT	Double	66	Belladonna 7CH and X-Ray 15CH (homeopathy medicines)	No statistical significance	NA	NA

[a] Smith and Nephew Healthcare, Hull, U.K.

Pts = patients; GM-CSF = granulocyte–macrophage colony–stimulating factor; NA = not available; RT = radiation therapy; RCT = randomized controlled trial; HR = hazard ratio; CI = confidence interval.

TABLE III Tumour type, radiation treatment regimen, adjuvant treatments, and additional care instructions

Reference	*Tumour type*	*Radiotherapy schedule*	*Adjuvant treatments*			*Additional skin care instruction*
			Chemotherapy		*Surgery*	
			Prior	*Concurrent*		
Prevention trials						
Washing practice						
Westbury *et al.*, 2000 [16]	Brain	High-dose (≥30 Gy) or low-dose (≤30 Gy)	NR	NR	NR	None
Roy *et al.*, 2001 [17]	Breast	45 Gy in 20 fr or 50 Gy in 25 fr, cobalt 60 or 6 MV	NR	NR	NR	None
Topical steroidal creams						
Boström *et al.*, 2001 [18]	Breast	56 Gy in 27 fr, 5 MV	Yes	NR	No	Non-blinded: both groups received emollient cream to use once daily
Schmuth *et al.*, 2002 [19]	Breast	56 Gy in 28 fr, 8 MV	Yes	Yes	Yes	No
Shukla *et al.*, 2006 [20]	Breast	50Gy in 25 fr, plus boost in some patients (16 Gy in 8 fr)	Yes	Yes	No	NR
Omidvari *et al.*, 2007 [21]	Breast	50 Gy in 25 fr, cobalt 60	Yes	Yes	No	Patients were instructed to clean skin before application of cream
Topical nonsteroidal creams—Aloe vera						
Olsen *et al.*, 2001 [22]	NR (gynecologic and brain excluded)	9–73 Gy	NR	NR	NR	None
Heggie *et al.*, 2002 [23]	Breast	50–64 Gy	Yes	Yes	Yes	Patients instructed to use mild baby soap on skin
Topical nonsteroidal creams—Biafine[a] *(trolamine salicylate) cream*						
Fisher *et al.*, 2000 [24]	Breast	50–64 Gy	NR	NR	No	None
Fenig *et al.*, 2001 [25]	Breast	50 Gy in 25 fr, 6 MV	Yes	No	No	If necessary, patients in control group received topical treatment
Szumacher *et al.*, 2001 [26]	Breast	50 Gy in 25 fr, 6 MV	Yes	No	Yes	None

TABLE III *(Continued)*

Reference	*Tumour type*	*Radiotherapy schedule*	*Adjuvant treatments*			*Additional skin care instruction*
			Chemotherapy		*Surgery*	
			Prior	*Concurrent*		
Topical nonsteroidal creams—Biafine[a] (trolamine salicylate) cream (Continued)						
Pommier *et al.,* 2004 [27]	Breast	Lumpectomy patients: 52 Gy in 26 fr, 5 MV Mastectomy patients: 46 Gy with optional 10-Gy boost	Yes	Yes	No	None[b]
Elliot *et al.,* 2006 [28]	Head-and-neck	≥50 Gy plus boost	Yes	NR	Yes	Patients instructed to cleanse with soap and warm water
Ribet *et al.,* 2008 [29]	Breast, head-and-neck	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]
Topical nonsteroidal creams—hyaluronidase-based						
Primavera *et al.,* 2006 [2]	Breast	50–70 Gy	NR	NR	No	No
Leonardi *et al.,* 2008 [30]	Breast	45 Gy in 20 fr, 6 MV, plus 0.25-Gy boost	Yes	NR	NR	No
Topical nonsteroidal creams—sucralfate or sucralfate derivatives						
Evensen *et al.,* 2001 [31]	Head and neck	50–70 Gy in 25–35 fr, 4–6 MV	NR	NR	NR	NR
Wells *et al.,* 2004 [32]	Breast, head-and-neck, anorectal	>40 Gy	NR	NR	NR	Patients instructed to wash with unperfumed soap
Topical nonsteroidal creams—miscellaneous creams						
Momm *et al.,* 2003 [33]	Head-and-neck	50–74 Gy in 25 fr, 6 MV	NR	No	No	For grade III/IV lesions, treatment was stopped and a wound care program was started
Röper *et al.,* 2003 [34]	Breast	50–50.4 Gy in 25 fr, 6 MeV	Yes	NR	No	Patients instructed to wash skin and note skin marks
Graham *et al.,* 2004 [35]	Breast	50 Gy in 25 fr, 6 MV (plus 10-Gy boost in 5 fr in some)	Yes	NR	Yes	NR

TABLE III *(Continued)*

Reference	*Tumour type*	*Radiotherapy schedule*	*Adjuvant treatments*			*Additional skin care instruction*
			Chemotherapy		*Surgery*	
			Prior	*Concurrent*		
Topical nonsteroidal creams—miscellaneous creams (Continued)						
Enomoto *et al.*, 2005 [36]	Breast	50–54 Gy plus 9- to 10-Gy boost	Yes	NR	NR	Patients instructed to use *Aloe vera* and vitamin E after treatments
Ma *et al.*, 2007 [37]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]
Matceyevsky *et al.*, 2007 [38]	Head-and-neck	XRT group: 56–70 Gy, 6 MV and 12 MV; control: 50–75 Gy, 6–12 MeV	Yes	NR	Yes	NR
Systemic interventions—amifostine						
Dunst *et al.*, 2000 [39]	Stage II/III rectal	56 Gy in 31 fr	Yes	Yes	Yes	NR
Kouvaris *et al.*, 2002 [40]	Vulvar	55.8–68 Gy, 6 MV	NR	NR	NR	NR
Systemic interventions—oral enzymes						
Dale *et al.*, 2001 [41]	Uterine, cervical	Uterine: 50–60 Gy in 25 fr (brachytherapy boost of 20–30 Gy) Cervical: 50–60 Gy in 25–35 fr	NR	No	NR	Use of anti-inflammatory topical anesthetic or mucoprotectant was recorded
Gurjal *et al.*, 2001 [42]	Head-and-neck	50–70 Gy in 25–35 fr, cobalt 60	NR	Yes	NR	No
Systemic interventions—pentoxifylline						
Aygenc *et al.*, 2003 [43]	Head-and-neck	65–75 Gy in 30 fr	Yes	No	No	NR
Supplements						
Lin *et al.*, 2006 [44]	Head-and-neck	45–50 Gy in 25 fr	NR	NR	Yes	NR
Dressings						
Vuong *et al.*, 2003 [45]	Gastrointestinal, anal, and gynecologic	45–54 Gy in 25–30 fr	NR	NR	Yes	Patients instructed to use soap and water during course of pelvic RT; control group received sulfazadine when needed

TABLE III *(Continued)*

Reference	*Tumour type*	*Radiotherapy schedule*	*Adjuvant treatments*			*Additional skin care instruction*
			Chemotherapy		*Surgery*	
			Prior	*Concurrent*		
Mode of radiation delivery						
DeLand *et al.,* 2007 [3]	Breast	IMRT plus boost: 50.4 Gy plus 12.6- to 18-Gy boost, 4–10 MV	Yes	Yes	NR	Patients instructed to apply Aquaphor[d] ointment 3–4 times daily during treatment
Pignol *et al.,* 2008 [46]	Breast	50 Gy in 25 fr, 6 MV or mixed energies; or IMRT ± 16-Gy boost	NR	NR	NR	No
Management trials						
Topical steroidal creams						
Kouvaris *et al.,* 2001 [47]	Vulvar	55.8–68 Gy, 6 MV	Yes	NR	NR	Steroid creams used in both groups from beginning to end of treatment
Topical nonsteroidal creams						
Garcia *et al.,* 2007 [48]	Head-and-neck, breast, other	50–66 Gy	Yes	Yes	Yes	NR
Dressings						
Mak *et al.,* 2000 [49]	Neck, chest, axilla, perineum	NR	NR	Yes[e]	Yes[e]	Patients instructed to wash with 0.9% normal saline before application of dressing
MacMillan *et al.,* 2007 [50]	Breast, head-and-neck, anorectal	≥40 Gy	NR	NR	NR	Patients instructed to wash area with unperfumed soap
Vavassis *et al.,* 2008 [51]	Head and neck	60–72 Gy in 30–42 fr	NR	Yes	Yes	Patients instructed to clean area before treatment
Other						
Balzarini *et al.,* 2000 [52]	Breast	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]

[a] Ortho-McNeil Pharmaceuticals, Titusville, NJ, U.S.A.
[b] Physician-treated grade 2 or higher skin reaction.
[c] Unknown because of lack of complete article.
[d] Beiersdorf, St. Laurent, QC.
[e] Patients stratified into those who received chemotherapy and external-beam radiotherapy, and those who received external-beam radiotherapy alone.
NR = not reported; fr = fractions; XRT = external-beam radiotherapy; RT = radiotherapy; IMRT = intensity-modulated radiotherapy.

the study, no differences were found between the petrolatum group and the control group ($p = 0.027$).

None of the studies evaluating the use of topical corticosteroid agents noted a significant difference in pain or itching attributable to radiation.

3.1.3 Nonsteroidal Topical Creams

Aloe vera: Two RCTs assessed the efficiency of *Aloe vera* in preventing radiation-induced skin reactions [22,29]. In a single-blind trial, Olsen *et al.* [22] evaluated the use of mild soap plus *Aloe vera* against mild soap alone. At a cumulative dose of more than 2700 cGy, a protective effect of adding *Aloe vera* to mild soap was noted, although the difference was nonsignificant. In a large double-blind study by Heggie *et al.* [23], *Aloe vera* was compared with an aqueous cream. The aqueous cream was found to be significantly better at reducing dry desquamation and pain secondary to treatment.

Biafine Cream: Six studies assessed Biafine cream (Ortho–McNeil Pharmaceuticals, Titusville, NJ, U.S.A.) for the prevention of radiation-induced skin reactions [24–29]. Five of those trials compared Biafine with another topical agent [24,25,27–29], and one evaluated the efficacy of Biafine cream without a comparator product [26].

In a phase II study, Szumacher *et al.* [26] assessed the ability of Biafine cream to prevent grade 2 or greater radiation dermatitis (National Cancer Institute of Canada acute toxicity criteria) in women with breast cancer receiving concomitant adjuvant chemotherapy and radiation to the affected breast. After the 5-week course of radiotherapy, the skin reaction occurring with highest frequency was grade 2 reaction in 83% of patients (grade < 2: 15%; grade 3: 2%).

Fisher *et al.* [24] evaluated the use of Biafine cream against best supportive care in a multicentre RCT. Best supportive care was defined as "institutional preference" and included Aquaphor Healing Ointment (Beiersdorf Canada, St. Laurent, QC) and *Aloe vera* as the top two choices. In a similar large multicentre study, Elliot *et al.* [28] evaluated Biafine cream in the preventive and interventional settings against an institutional preference, which was different for each centre. Both trials reported no significant difference between Biafine cream and institutional preference for the prevention of radiation-induced skin reactions [24,28].

Fenig *et al.* [25] compared the efficacy of Biafine cream with that of Lipiderm cream (G-Pharm, Salisbury, U.K.) for preventing radiation dermatitis by evaluating the maximal level of skin reaction and the number of gaps in treatment. Those authors found no significant differences between the two treatment groups and a control group. However, they did note that 86% of patients reported no difficulty when using the Biafine or Lipiderm creams.

In a RCT, Ribet *et al.* compared the median time to emergence of the first objective signs of radiation dermatitis in patients using Biafine or Avène thermal spring water anti-burning gel (Pierre Fabre Dermo Cosmétique USA, Parsippany, NJ, U.S.A.) and found no significant differences between the groups [29].

In the largest of the six trials involving Biafine, Pommier *et al.* [27] examined the preventive effects of Biafine cream with those of calendula ointment and found a significant difference in the number of grade 2 or greater reactions (RTOG) in favour of calendula ointment (41% vs. 63%, $p < 0.001$). Those authors noted a difference in favour of the calendula-treated group for the mean maximal pain experienced ($p = 0.03$) and against the calendula ointment for the level of difficulty encountered in applying the cream (30% vs. 5%). The calendula ointment was recommended for use; however, the increased difficulty experienced by patients in the calendula group with application of the ointment meant that they were more likely to be noncompliant.

Hyaluronidase-Based Creams: Hyaluronic acid is thought to accelerate the healing process by stimulating fibroblasts and fibrin formation. Leonardi *et al.* [30] assessed the efficacy of Xclair (Align Pharmaceuticals, Berkeley Heights, NJ, U.S.A.), a water-based cream with barrier-forming, hydrating, and anti-inflammatory properties, against that of the vehicle alone in a double-blind randomized study of breast cancer patients receiving adjuvant radiation. Those authors found a highly significant difference between the two groups in the maximum grade of radiation dermatitis ($p < 0.0001$) after 3 weeks of radiation treatment. Their study also noted that patients in the Xclair group felt a decreased burning sensation ($p = 0.039$). There were no statistical differences noted for pain or itching.

Primavera *et al.* [2] used patients as their own controls in assessing the effectiveness of Xclair at managing radiation-induced skin reactions. Those authors found that the areas treated with Xclair showed a significantly lower NCI grade of dermatitis than did areas treated with vehicle alone at week 4 of radiation ($p = 0.031$). The mean erythema scores were significantly lower in the Xclair treatment areas than in the vehicle areas at weeks 4, 5, and 6 of radiation ($p = 0.01$, 0.005, 0.03 respectively). No significant differences were found for pain and itch scores. Notably, 65% of patients preferred Xclair cream to the vehicle; only 10% favoured the vehicle.

Sucralfate or Sucralfate Derivatives: Sucralfate is a persulfated disaccharide in complex with aluminum [31]. Two randomized trials evaluated the effects of sucralfate cream over control [31,32]. In an internal control setting, Evensen *et al.* [31] randomized areas of the treatment field to sucralfate or to vehicle. Those authors did not identify a significant difference in the incidence of erythema, desquamation, pain, or itching. In a factorial design, Wells *et al.* [32] compared

sucralfate cream with aqueous cream and with no cream. They found no reliable differences in the severity of the reaction or in the level of discomfort between the groups.

Miscellaneous Creams: In a randomized study of breast cancer patients, Enomoto *et al.* [36] compared RayGel, a gel formulated by a naturopathic physician, with a placebo. Both groups received instruction on the institution's standard skin care recommendation, which included the use of *Aloe vera* gel and vitamin E after radiation treatments in addition to RayGel or placebo. Enomoto *et al.* found a trend toward lower worst skin reaction scores for the RayGel group, but statistical significance was not achieved.

Using internal controls, Graham *et al.* compared Cavilon No Sting Barrier Film (3M, St. Paul, MN, U.S.A.) with sorbolene cream for the prevention of moist desquamation with breast radiation. Treatment areas were divided into medial and lateral components and each component was randomized to one of the topical agents. A significantly lower skin toxicity score was found on breast areas treated with the No Sting Barrier Film ($p = 0.005$). Pain was evaluated, but was not found to be significantly different between the groups [35].

Röper *et al.* [34] alternatively assigned patients to use Thêta-Cream (TheraCosm, Dellstedt, Germany) or Bepanthol lotion (Bayer Schering Pharma, Wilmington, DE, U.S.A.) and reported no significant differences between the groups.

Matceyevsky *et al.* [38] evaluated the efficacy of Solaris lotion (Eugene–Perma, Paris, France) over a control in the prevention of dermatitis attributable to radiochemotherapy in head-and-neck cancer patients. That trial did not find any differences in the severity of skin reaction between the treatment arms; however, a difference in favour of the Solaris lotion was noted in the number of breaks from treatment ($p = 0.034$).

A comparison of moist skin care (0.3% urea lotion) versus dry skin care (powder) after radiotherapy was conducted by Momm *et al.* [33] in a multicentric study. Those authors found that significantly more patients treated with dry skin care (56% vs. 22% using lotion) experienced a grade 3 skin reaction (RTOG, $p = 0.0007$). This study also noted that a greater number of patients in the dry skin care group were hospitalized because of the severity of their skin reaction (28% vs. 10% in the moist skin care group), but that finding was not statistically significant.

The last trial was performed by Ma *et al.* [37], who studied a Chinese remedy, *lian bai* liquid in patients without a skin reaction (prevention group) and in those who presented with a grade 3 reaction (NCI CTC, treatment group). Both groups were also compared with controls. *Lian bai* liquid was effective in reducing the incidence of skin reactions in the prevention group as compared with controls ($p < 0.01$).

3.1.4 Systemic Interventions

Amifostine: Amifostine is a thiol derivative that has demonstrated radioprotective effects in animal experiments [39]. One retrospective study [47] and one nonrandomized clinical trial [39] evaluated amifostine as a cytoprotective agent against acute radiation-induced skin reactions.

Kouvaris *et al.* [47] retrospectively compared patients treated with intravenous amifostine against historical controls. Those authors found that patients who received amifostine had dermatitis of significantly reduced severity ($p < 0.001$), a lower mean gross dermatitis score ($p < 0.001$), and a lesser mean treatment interruption time ($p < 0.001$).

Dunst *et al.* [39] assessed the efficacy of amifostine in patients receiving radiochemotherapy for rectal cancer. The maximum grade of erythema was higher in patients who did not receive amifostine (1.46 ± 0.64 vs. 0.87 ± 0.52, $p = 0.009$). However, maximum nausea scores were significantly higher in patients who received amifostine (0.27 ± 0.46 vs. 0.93 ± 0.53, $p = 0.002$).

Oral Enzymes: Two RCTs examined the efficacy of oral hydrolytic enzymes [41,42]. Both trials compared Wobe–Mugos enzyme with no treatment; the study patients had either head-and-neck cancer [42] or cervical or uterine cancer [41]. Gurjal *et al.* [42] reported that the maximum extent of skin reaction was lower in the enzyme-treated group ($p < 0.0001$). Dale *et al.* [41] observed a lower average maximum extent of acute reaction in patients who were randomized to receive the enzyme ($p < 0.001$). Neither trial identified a difference in pain or itching between the two groups.

Pentoxifylline: One study by Aygenc *et al.* [43] assessed the effect of prophylactic pentoxifylline on radiation-induced toxicities. Pentoxifylline is a drug that is currently used to treat a variety of vaso-occlusive disorders. It is known to improve microcirculation by increasing the flexibility of red blood cells. Aygenc and colleagues found no significant difference in the maximum acute skin reaction score between a pentoxifylline group and a control group; however, a significant difference in the maximum skin reaction score for late skin changes, 8 weeks post radiotherapy, was identified (average maximal score: 2.96 vs. 3.44, $p < 0.05$).

Supplements: One double-blind RCT in head-and-neck cancer patients compared a zinc supplement with placebo [44]. Grade 2 dermatitis (RTOG) appeared earlier in the placebo group than in the group supplemented with zinc ($p = 0.017$). A similar finding was noted with grade 3 dermatitis ($p = 0.0092$). Two weeks post radiotherapy, both groups demonstrated similar improvements in relation to dermatitis [44].

3.1.5 Dressings

One trial studied the effect of silver-leaf nylon dressing, which has been shown to have antimicrobial properties and to enhance healing in burn and skin grafts. Vuong *et al.* [45] examined 15 patients receiving radiation to the perineum who were instructed to wear the dressing from the initiation of radiation until 2 weeks post radiation. Results were compared with data from historical controls. The mean dermatitis grades (RTOG) were significantly lower in the dressing group than in the control group, and the benefit was thought to be attributable to the antimicrobial properties of the dressings (mean RTOG grade: 1.16 vs. 2.62, $p < 0.0001$).

3.1.6 Mode of Radiation Delivery

Two studies examined different methods of delivering radiation. One trial evaluated intensity-modulated radiation therapy (IMRT) for adjuvant therapy of breast cancer in a multicentric double-blind RCT. The goal was to observe whether this novel technique could deliver a more homogenous radiation dose throughout the breast. Theoretically, this approach would reduce the occurrence of higher spot doses of radiation, leading to a lower incidence of skin reaction. This trial, performed by Pignol *et al.* [46], found that, as compared with a standard method of delivering radiotherapy, breast IMRT significantly reduced the number of patients who experienced moist desquamation during or up to 6 weeks after treatment (31.2% vs. 47.8%, $p = 0.002$).

DeLand *et al.* [3] assessed the use of light-emitting diode (LED) photomodulation after each series of IMRT in breast cancer patients. The results were compared with data from historical controls who received similar doses of IMRT without the LED treatment. Those authors found that treatment with LED immediately after IMRT significantly lowered the grade of skin reaction (5.3% grade 2 reaction in LED group vs. 85.7% grade 2–3 reaction in non-LED group, $p < 0.0001$).

3.2 Outcomes: Management Trials

3.2.1 Topical Colony-Stimulating Factors

One nonrandomized open study by Kouvaris *et al.* [40] compared use of betamethasone alone with the use of gauze impregnated with a granulocyte–macrophage colony–stimulating factor (GM-CSF) in addition to betamethasone. The authors found that the grades of skin reaction were significantly lower ($p = 0.008$) and the healing time significantly shorter ($p = 0.02$) in the GM-CSF group. Grade 3 and 4 reactions, evaluated using the Subjective Objective Management Analytic (SOMA) grading system, were significantly fewer in the GM-CSF group ($p = 0.014$). Kouvaris and colleagues also found that the time interval of treatment interruption was significantly shorter in patients who received the GM-CSF (5.17 ± 1.76 days vs. 6.57 ± 2.30 days, $p = 0.037$) and that pain relief occurred significantly sooner after GM-CSF application (3.12 ± 1.42 days vs. 5.48 ± 1.59 days, $p = 0.0017$) [40]. This study used a "sum of gross dermatitis score" that was evaluated by adding the dermatitis score (RTOG criteria) to the pain score (SOMA grading system). Although the summed score was based on validated measurement tools, the summation method itself has not been validated for assessing radiation dermatitis.

3.2.2 Nonsteroidal Topical Cream

Garcia *et al.* [48] conducted a phase I trial evaluating the efficacy of superoxide dismutase (SOD) to treat grade 2 dermatitis (RTOG) in varying cancer types. Those authors demonstrated a 77.1% response at the completion of radiation treatment (17.5% complete response; 59.6% partial response) and no worsening of the condition at the end of the 12-week study period. No acute toxicities related to SOD were reported in the trial [48].

3.2.3 Dressings

Three trials evaluated the effects of dressings on managing radiation dermatitis [49–51].

MacMillan *et al.* [50] studied a hydrogel (moist) dressing compared with a dry dressing in the management of moist desquamation. Patients were randomized to one of the two dressing types. All were instructed to wash the treatment area and were given a supply of unperfumed simple soap. Compared with patients who were allocated to the dry dressings, patients randomized to the gel dressings were significantly more likely to use their dressings (93.1% vs. 63.1%, $p = 0.002$). Patients assigned to the gel dressings also had a significantly longer healing time (defined by return to a grade 2 or lesser reaction, $p = 0.03$). No differences were observed in pain or itching scores between the two groups [50].

Using internal controls, Vavassis *et al.* [51] compared silver-leaf nylon dressings with silver sulfadiazine cream in a small trial in patients receiving radiation for head-and-neck cancer. Those authors found no significant improvement in RTOG skin toxicity grade; however, a reduction in the severity of the within-grade skin reaction was observed with the silver-leaf dressing ($p = 0.035$), and pain scores were subjectively superior for the silver-leaf dressing.

In a RCT, Mak *et al.* [49] studied the effectiveness of hydrocolloid dressings over gentian violet in the management of moist desquamation. There was no difference between the groups in healing time, but wound size and wound pain were significantly less with gentian violet. However, gentian violet treatment received significantly lower ratings for dressing comfort and aesthetic acceptance [49].

3.2.4 Other

One double-blind RCT by Balzarini *et al.* [52] assessed the effects of Belladonna 7CH and X-Ray 15CH (homeopathic medicines), in the treatment of radiation

dermatitis. Skin colour, warmth, swelling, and pigmentation were assessed and combined to give an "index of total severity." The differences in the index scores during the radiotherapy treatments were not statistically significant, but the differences in scores during the recovery period (time after radiation) showed a significant benefit for the Belladonna 7CH over the X-Ray 15CH [52].

As mentioned earlier, the trial by Ma *et al.* [37] evaluated the effect of the Chinese remedy *lian bai* liquid on patients who presented with grade 3 skin reaction (NCI CTC) and compared that group (and a prevention group) with controls. *Lian bai* liquid decreased the time to wound healing (11.07 ± 2.21 days vs. 18.08 ± 1.76 days, $p < 0.01$).

4. DISCUSSION

4.1 Prevention of Acute Radiation-Induced Skin Reactions

Overall, there is a general lack of support in literature for choosing Biafine over other agents in prevention of acute radiation-induced skin reactions. There is some evidence to suggest that topical corticosteroid agents may be beneficial in decreasing the incidence of radiation dermatitis, especially grade 3 and 4 reactions [19,21]. The evidence for the use of nonsteroidal topical agents is conflicting: some trials were positive for nonsteroidal agents [30,33,35,37]; others showed no statistical difference [34,36,38]. The evidence did not support the use of *Aloe vera* [22,23] or sucralfate cream [31,32]. There was some evidence to suggest that LED treatment, pentoxifylline, silver-leaf dressings, washing with soap and water, and zinc supplements help to prevent radiation-induced skin reactions [3,17,43–45]. A large multicentric RCT comparing breast IMRT with standard breast radiation treatment showed a significant reduction in moist desquamation in the IMRT group.

Overall, the many trials evaluating a large variety of products and methods for the prevention of acute radiation-induced skin reactions do not support a general consensus on a superior product that should be used in this setting. Future trials should focus on comparing one or two of the agents for which some benefit is indicated, so as to better establish their efficacy. Such trials should take into account subjective patient evaluation of the product, compliance, and quality of life, because these factors are crucial when recommending the widespread use of one agent.

4.2 Management of Acute Radiation-Induced Skin Reactions

The treatments that were assessed for the management of radiation-induced skin reactions include topical steroid creams, nonsteroidal creams, dressings, and herbal remedies. No two trials evaluated the same agent or treatment, making it difficult to compare results. Only three of the trials showed a significant difference: one in favour of a corticosteroid cream, one favouring a nonsteroidal cream, and one for a dressing. However, all three of these trials were small and had limitations that prevent the generalizability of the results. The small number and large variety of trials make it difficult to draw any conclusions concerning the management of radiation skin reactions. A greater number of trials assessing treatments for radiation-induced skin reactions, especially moist desquamation and ulceration reactions (grades 3 and 4), must be performed.

5. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

To date, attempts to prevent or manage acute radiation dermatitis appear somewhat haphazard, trying various creams and lotions, systemic interventions, and radiation delivery methods without paying a great deal of attention to the underlying pathophysiology. Future efforts must be more systematic. They must incorporate new knowledge regarding radiation-induced dermatitis so that the pathophysiologic process set in motion by the radiation can either be prevented or attenuated, and in situations in which damage cannot be averted, the healing process accelerated. We make these suggestions:

- The goal of the intervention—that is, prevention or treatment—must be clearly distinguished in advance.
- Interventions must attempt to take into account the pathophysiologic process of radiation-induced dermatitis.
- Further work is required to develop and validate assessment tools that are sensitive to changes in skin damage resulting from radiation over time. Prevention and treatment interventions will likely require different tools. These tools must incorporate patient-reported outcome measures to better reflect the patient experience.
- Further study is required to determine differences in the risk of radiation-induced skin toxicity for various tumour types and anatomic areas. A variety of assessment tools may need to be developed, depending the level, or risk and severity, of the expected reaction.
- Consensus on the appropriate endpoints of interest both for prevention and for management trials must be developed.

6. CONFLICT OF INTEREST DISCLOSURES

This research was generously supported by Align Pharmaceuticals. All authors declare that no financial conflict of interest exists.

7. REFERENCES

1. Maddock–Jennings W, Wilkinson JM, Shillington D. Novel approaches to radiation-induced skin reactions: a literature review. *Complement Ther Clin Pract* 2005;11:224–31.
2. Primavera G, Carrera M, Berardesca E, Pinnaró P, Messina M, Arcangeli G. A double-blind, vehicle controlled clinical study to evaluate the efficacy of MAS065D (Xclair), a hyaluronic acid–based formulation, in the management of radiation-induced dermatitis. *Cutan Ocul Toxicol* 2006;25:165–71.
3. DeLand MM, Weiss RA, McDaniel DH, Geronemus RG. Treatment of radiation-induced dermatitis with light-emitting diode (LED) photomodulation. *Lasers Surg Med* 2007;39:164–8.
4. MacBride SK, Wells ME, Hornsby C, Sharp L, Finnila K, Downie L. A case study to evaluate a new soft silicone dressing, Mepilex Lite, for patients with radiation skin reactions. *Cancer Nurs* 2008;31:E8–14.
5. McQuestion M. Evidence based skin care management in radiation therapy. *Semin Oncol Nurs* 2006;22:163–73.
6. Bolderston A, Lloyd NS, Wong RK, Holden L, Robb–Blenderman L. The prevention and management of acute skin reactions to radiation therapy: a systematic review and practice guideline. *Support Care Cancer* 2006;14:802–17.
7. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol* 2006;54:28–46.
8. Boström A, Lindman H, Swartling C, Berne B, Bergh J. Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study. *Radiother Oncol* 2001;59:257–65.
9. Vuong T, Franco E, Lehnert S, *et al.* Silver leaf nylon dressing to prevent radiation dermatitis in patients undergoing chemotherapy and external beam radiotherapy to the perineum. *Int J Radiat Oncol Biol Phys* 2004;59:809–14.
10. Lavery BA. Skin care during radiotherapy: a survey of UK practice. *Clin Oncol (R Coll Radiol)* 1995;7:184–7.
11. D'haese S, Bate T, Claes S, Boone A, Vanvoorden V, Efficace F. Management of skin reactions during radiotherapy: a study of nursing practice. *Eur J Cancer Care (Engl)* 2005;14:28–42.
12. Harper JL, Franklin LE, Jenrette JM, Aguero EG. Skin toxicity during breast irradiation: pathophysiology and management. *South Med J* 2004;7:989–93.
13. Schratter–Sehn AU, Brinda K, Kahrer M, Novak M. Improvement of skin care during radiotherapy. *Onkologie* 2001;24:44–6.
14. Schreck U, Paulsen F, Bamberg M, Budach W. Intraindividual comparison of two different skin care conceptions in patients undergoing radiotherapy of the head-and-neck region. Creme or powder? *Strahlenther Onkol* 2002;178:321–9.
15. Hu YR, Wu CQ, Liu YJ, *et al.* Clinical observation on effect of *shenqi fanghou* recipe in preventing and treating radiation injury in patients with head and neck tumor [Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2005;25:623–5.
16. Westbury C, Hines F, Hawkes E, Ashley S, Brada M. Advice on hair and scalp care during cranial radiotherapy: a prospective randomized trial. *Radiother Oncol* 2000;54:109–16.
17. Roy I, Fortin A, Larochelle M. The impact of skin washing with water and soap during breast irradiation: a randomized study. *Radiother Oncol* 2001;58:333–9.
18. Boström A, Lindman H, Swartling C, Berne B, Bergh J. Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study. *Radiother Oncol* 2001;59:257–65.
19. Schmuth M, Wimmer MA, Hofer S, *et al.* Topical corticosteroid therapy for acute radiation dermatitis: a prospective, randomized, double-blind study. *Br J Dermatol* 2002;146:983–91.
20. Shukla PN, Gairola M, Mohanti BK, Rath GK. Prophylactic beclomethasone spray to the skin during postoperative radiotherapy of carcinoma breast: a prospective randomized study. *Indian J Cancer* 2006;43:180–4.
21. Omidvari S, Saboori H, Mohammadianpanah M, *et al.* Topical betamethasone for prevention of radiation dermatitis. *Indian J Dermatol Venereol Leprol* 2007;73:209–15.
22. Olsen DL, Raub W Jr, Bradley C, *et al.* The effect of *Aloe vera* gel/mild soap versus mild soap alone in preventing skin reactions in patients undergoing radiation therapy. *Oncol Nurs Forum* 2001;28:543–7.
23. Heggie S, Bryant GP, Tripcony L, *et al.* A phase III study on the efficacy of topical *Aloe vera* gel on irradiated breast tissue. *Cancer Nurs* 2002;25:442–51.
24. 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;48:1307–10.
25. Fenig E, Brenner B, Katz A, *et al.* Topical Biafine and Lipiderm for the prevention of radiation dermatitis: a randomized prospective trial. *Oncol Rep* 2001;8:305–9.
26. Szumacher E, Wighton A, Franssen E, *et al.* Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *Int J Radiat Oncol Biol Phys* 2001;51:81–6.
27. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. Phase III randomized trial of *Calendula officinalis* compared with trolamine for the prevention of acute dermatitis during radiation for breast cancer. *J Clin Oncol* 2004;22:1447–53.
28. Elliot EA, Wright JR, Swann S, *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;24:2092–7.
29. Ribet V, Salas S, Levecq JM, *et al.* Interest of a sterilised antiburning gel in radiation dermatitis: results of a comparative study [French]. *Ann Dermatol Venereol* 2008;1:5–10.
30. Leonardi MC, Gariboldi S, Ivaldi GB, *et al.* A double-blind randomized, vehicle-controlled clinical study to evaluate the efficacy of MAS065D in limiting the effects of radiation on the skin: interim analysis. *Eur J Dermatol* 2008;18:317–21.
31. Evensen JF, Bjordal K, Jacobsen AB, Løkkevik E, Tausjø JE. Effects of Na–sucrose octasulfate on skin and mucosa reactions during radiotherapy of head and neck cancer. *Acta Oncol* 2001;40:751–5.
32. Wells M, Macmillan M, Raab G, *et al.* Does aqueous or sucralfate cream affect the severity of erythematous radiation skin reactions? *Radiother Oncol* 2004;73:153–62.

33. Momm F, Weissenberger C, Bartelt S, Henke M. Moist skin care can diminish acute radiation-induced skin toxicity. *Strahlenther Onkol* 2003;10:708–12.
34. Röper B, Kaisig D, Auer F, Mergen E, Molls M. Thêta-Cream versus Bepanthol lotion in breast cancer patients under radiotherapy. A new prophylactic agent in skin care? *Strahlenther Onkol* 2004;180:315–22.
35. Graham P, Browne L, Capp A, *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;58:241–6.
36. Enomoto TM, Johnson T, Peterson N, Homer L, Walts D, Johnson N. Combination glutathione and anthocyanins as an alternative for skin care during external-beam radiation. *Am J Surg* 2005;189:627–31.
37. Ma H, Zhang X, Bai M, Wang X. Clinical effects of *lianbai* liquid in prevention and treatment of dermal injury caused by radiotherapy. *J Tradit Chin Med* 2007;27:193–6.
38. Matceyevsky D, Hahoshen NY, Vexler A, Noam A, Khafif A, Ben-Yosef R. Assessing the effectiveness of Dead Sea products as prophylactic agents for acute radiochemotherapy-induced skin and mucosal toxicity in patients with head and neck cancers: a phase 2 study. *Isr Med Assoc J* 2007;9:439–42.
39. Dunst J, Semlin S, Pigorsch S, Müller AC, Reese T. Intermittent use of amifostine during postoperative radiochemotherapy and acute toxicity in rectal cancer patients. *Strahlenther Onkol* 2000;176:416–21.
40. Kouvaris J, Kouloulias V, Kokakis J, Matsopoulos G, Myrsini B, Vlahos L. The cytoprotective effect of amifostine in acute radiation dermatitis: a retrospective analysis. *Eur J Dermatol* 2002;12:458–62.
41. Dale PS, Tamhankar CP, George D, Daftary GV. Co-medication with hydrolytic enzymes in radiation therapy of uterine cervix: evidence of the reduction of acute side effects. *Cancer Chemother Pharmacol* 2001;47(suppl):S29–34.
42. Gujral MS, Patnaik PM, Kaul R, *et al.* Efficacy of hydrolytic enzymes in preventing radiation therapy–induced side effects in patients with head and neck cancers. *Cancer Chemother Pharmacol* 2001;47(suppl):S23–8.
43. Aygenc E, Celikkanat S, Kaymakci M, Aksaray F, Ozdem C. Prophylactic effect of pentoxifylline on radiotherapy complications: a clinical study. *Otolaryngol Head Neck Surg* 2004;130:351–6.
44. Lin LC, Que J, Lin LK, Lin FC. Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. *Int J Radiat Oncol Biol Phys* 2006;65:745–50.
45. Vuong T, Franco E, Lehnert S, *et al.* Silver leaf nylon dressing to prevent radiation dermatitis in patients undergoing chemotherapy and external beam radiotherapy to the perineum. *Int J Radiat Oncol Biol Phys* 2004;59:809–14.
46. 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;26:2085–92.
47. Kouvaris JR, Kouloulias VE, Plataniotis GA, Balafouta EJ, Vlahos LJ. Dermatitis during radiation for vulvar carcinoma: prevention and treatment with granulocyte–macrophage colony–stimulating factor impregnated gauze. *Wound Repair Regen* 2001;9:187–93.
48. Garcia AM, Carrizosa MCL, Ocaña CV, *et al.* Superoxide dismutase (SOD) topical use in oncologic patients: treatment of acute cutaneous toxicity secondary to radiotherapy. *Clin Transl Oncol* 2008;10:163–7.
49. Mak SS, Molassiotis A, Wan WM, Lee IY, Chan ES. The effects of hydrocolloid dressing and gentian violet on radiation-induced moist desquamation wound healing. *Cancer Nurs* 2000;23:220–9.
50. Macmillan MS, Wells M, MacBride S, Raab GM, Munro A, MacDougall H. Randomized comparison of dry dressings versus hydrogel in management of radiation-induced moist desquamation. *Int J Radiat Oncol Biol Phys* 2007;68:864–72.
51. Vavassis P, Gelinas M, Chabot Tr J, Nguyen-Tân PF. Phase 2 study of silver leaf dressing for treatment of radiation-induced dermatitis in patients receiving radiotherapy to the head and neck. *J Otolaryngol Head Neck Surg* 2008;37:124–9.
52. Balzarini A, Felisi E, Martini A, De Conno F. Efficacy of homeopathic treatment of skin reactions during radiotherapy for breast cancer: a randomised, double-blind clinical trial. *Br Homeopath J* 2000;89:8–12.

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