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REVIEW

Topical treatment of radiation-induced dermatitis: current issues and potential solutions

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Abstract

Approximately 95% of patients receiving radiotherapy (RT) will ultimately develop radiation-induced dermatitis (RID) during or after the course of treatment, with major consequences on quality of life and treatment outcomes. This paper reviews the pathophysiology of RID and currently used topical products for the prevention and treatment of RID. Although there is no consensus on the appropriate management, recent evidence suggests that the use of topical products supports to protect and promote tissue repair in patients with RID. Basic recommendations include advice to wear loose clothing, using electric razors if necessary, and avoiding cosmetic products, sun exposure or extreme temperatures. Based on mechanisms involved and on the clinical characteristics of oncological patients, the profile of the ideal topical product for addressing RID can be designed; it should have limited risk of adverse events, systemic adsorption and drug–drug interactions, should be characterized by multiple clinical activities, with a special focus on localized pain, and should have a careful formulation as some vehicles can block the RT beam.

Keywords: pain, quality of life, radiation-induced dermatitis, radiotherapy, skin toxicity, topical treatment.

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Introduction

Radiation-induced dermatitis (RID) is a very common side effect that is almost universally experienced by patients undergoing radiotherapy (RT) for cancer treatment. RID results from cutaneous or subcutaneous lesions due to external beam radiation. Indeed, it has been estimated that approximately 95% of patients receiving RT will ultimately develop RID during or after the course of treatment, with major consequences on quality of life and adherence to RT treatments, thereby affecting clinical outcomes.[1–3] However, at present, there is no consensus on the appropriate management of this condition. Therefore, there is urgent need for increased knowledge to guarantee a range of therapeutic options available for the treatment of RID.[1]

Recent evidence suggests that topical products may be used to protect and promote tissue repair in patients with RID, including within the prophylactic setting.[4,5]

The aim of this paper is to discuss current knowledge on RID and propose targets for the prevention/treatment of this condition. On these bases, the characteristics of the 'ideal' compound to address this side effect will be described.

Manuscripts for consideration in the present paper were retrieved via a PubMed search, using pertinent keywords (e.g. radiation-induced dermatitis). Papers were then selected for inclusion according to their relevance to the topic, as judged by the authors. The reference lists of the papers were also browsed to identify other suitable publications. Papers from personal collections of literature of the authors were also considered.

RID: basic concepts

Clinical manifestations

Key symptoms of RID include pain, ulceration, swelling, itching, burning, and physical and psychological discomfort. Opportunistic infections may also arise.[6–9] While these lesions may resolve over time, they can deeply influence quality of life and also limit the duration of treatment and the dose of radiation delivered, all of which have important consequences on therapy outcomes.[4,10]

The severity of RID is usually assessed by the physician according to standard instruments, such as the Common Terminology Criteria for Adverse Events (CTCAEs) scale (versions 2.0, 3.0, 4.0, or 4.03) or the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scale.[2] However, patient-reported outcome (PRO) tools (e.g. Skindex-16 or Brief Pain Inventory [BPI]) are sometimes used in clinical practice together with the CTCAE scale.[2] Up to 90% of patients will develop mild (grade 1) skin reactions, and approximately 20% of patients will develop severe forms of this condition.[11] Remarkably, concomitant systemic treatments (e.g. platinum-based regimens, cetuximab, 5-fluorouracil), administered to a good proportion of patients undergoing RT, can enhance the severity of RID.[2]

RID is characterized by an acute reaction when it occurs around the time of therapy and either chronic or late onset when it appears months or years after the end of treatment. Early skin reactions to RT usually occur within days to weeks from initiation, while late changes can happen even months or years after the completion of a RT course.

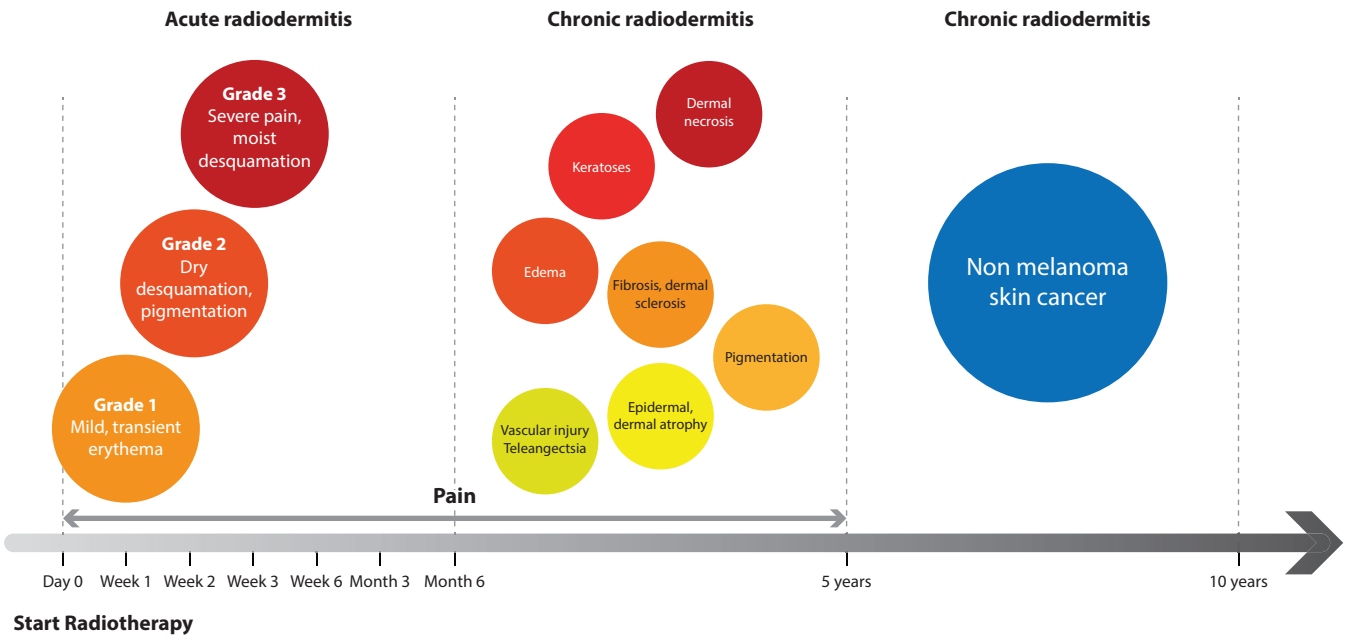
Usually, an acute phase of RID is defined by skin lesions that appear within 90 days from the start of treatment. Injury can first manifest as a transient erythema that may be reported as early as within the first 24 hours after the initiation of RT and is resolved within a few days (Figure 1).[12,13] Later, during weeks 2–4 of therapy, a more sustained generalized erythema and the onset of pain may be reported often associated with other skin changes, such as dryness and hyperpigmentation. During weeks 3–6 (from the start of therapy), dry desquamation associated with pain, pruritus, and scaling can develop if the cumulative radiation dose reaches 20 Gy, and moist desquamation may occur if total radiation dose to the skin is ≥40 Gy.[14] In this latter case, temporary interruption of RT, until the area is able to re-epithelialize, may be necessary.[15]

Chronic skin reactions to RT develop more than 90 days after the completion of radiation treatment.[12] These reactions include vascular injury resulting in telangiectasia, epidermal thinning, dermal atrophy, pigmentation, fibrosis, edema, keratosis, and, even, dermal necrosis. Moreover, patients show increased risk for the development of non-melanotic cutaneous malignancies in the course of their life.

Pathophysiology

Injury from RT derives from the generation of free radicals and reactive oxygen species in the rapidly dividing cells of

Figure 1. Progression of clinical manifestations and symptoms of RID.



RID, radiation-induced dermatitis.

the basal layer and underlying dermis.[12] Within a few hours from the start of treatment, this action decreases the number of functional stem cells, induces changes in endothelial cells, and promotes inflammation by the release of several cytokines and chemokines, most notably interleukin (IL)-1α, IL-1β, tumor necrosis factor-α, IL-6, IL-8, C–C motif chemokine ligand 4 (CCL4), C–X–C motif chemokine ligand 10 (CXCL10), and C–C motif chemokine ligand 2 (CCL2).[15,16] Over the subsequent 2–4 weeks, a sustained generalized erythema develops, most likely associated with local degeneration and edema, resulting from infiltration of leukocytes into the irradiated skin, which is a 'hallmark' of radiation-induced skin injury. Dryness and epilation, often observed at this time of the course of RID, result from the destruction of sebaceous glands and hair follicles.[17–19]

Moreover, differing from other forms of mechanical or chemical damage to the skin, RT-induced damage is repetitive and accumulates over the course of treatment, leading also to a delayed disruption of the epidermal barrier. Indeed, chronic effects induced by RT comprise changes of the vasculature and connective tissue of the cutaneous and subcutaneous layers. Remodeling of epithelium may then lead to the formation of telangiectasias.[20] With accumulating doses of radiation, if the healing process based on growth factors, such as fibroblast growth factor (FGF) or epidermal growth factor (EGF), is impaired,[21] melanocytes and fibroblasts can be destroyed, causing hypopigmentation and atrophy of the derma.[12]

Epidemiology of RID

RID is a widespread, although often neglected, side effect of RT. Indeed, at least 50% of patients with any type of cancer receive some form of RT during their disease history.[4] This prevalence is even higher in patients with head and neck and breast cancer: it has been estimated that 80–90% of all patients with head and neck cancer receiving RT develop RID, and 25% develop severe skin reactions.[22] In the breast cancer setting, one of the most widespread forms of cancer worldwide, 45% of patients receive RT, and the wide majority of them (74–100%) report RID.[23] Furthermore, chronic RID develops in one out of three patients and can appear up to 10 years after the completion of RT.[24] As >80% of all women treated for breast cancer survive for ≥10 years, the burden of chronic RID is mounting.[25] The risk of developing RID depends on various treatment-related factors: the radiation dose during a single delivery, the total dose, the duration of exposure, the volume of the treated area, and the combination with other therapies, such as chemotherapy.[26] Furthermore, RID can be influenced by patient-related factors that include high body mass index (BMI), smoking, nutritional status, pre-existing skin diseases, such as psoriasis, and genetic susceptibility.

Skin damage has also been associated with chemotherapy, although incidence of this event has not been precisely estimated.[26] Of note, radiation recall dermatitis is an acute inflammatory skin reaction occurring in a skin area previously exposed to RT and triggered by subsequent intake of a drug, most commonly a chemotherapeutic agent. The incidence of radiation recall dermatitis cannot be precisely determined, as most evidence comes from case report studies. Nevertheless, the effect has been reported in association with the use of several antineoplastic drugs.[27]

The rationale and bases for management of RID

As of today, management of RID is still based on preliminary evidence.[4] Indeed, at present, it is not possible to propose any firm recommendation to prevent or reduce RID.[2,4,20,28,29]

However, some basic recommendations can be made, according to the Multinational Association of Supportive Care in Cancer (MASCC) guidelines[20]: patients should be advised to wear loose clothing, use electric razors (if necessary), and avoid cosmetic products, sun exposure or extreme temperatures.[12] Moreover, regular skin care assessment is mandatory during RT treatments.

In multimorbid, often polytreated and frail patients, like many in the oncological population, topical substances may represent the best initial option for treatment of skin toxicity.[1,30–32]

It is commonly accepted that daily topical treatment could be useful if started right from the beginning of RT to prevent the onset of RID.[4]

Available information on currently used topical approaches for the prevention and treatment of RID is presented in Table 1, while an overview of those approaches is presented in the following section.

Different treatments for RID: an overview

Washing

Following standard hygiene practices is undoubtedly the most advantageous choice in the management of RID. Two well-conducted randomized controlled trials (RCTs) showed that washing with mild soap and lukewarm water reduces itching and RID severity.[33,34]

Dressings

Silver sulfadiazine, a topical antibacterial, is used as cream for second- and third-degree burns. This molecule is also endowed with anti-inflammatory properties and barrier-enhancing functions, thereby contributing to protect the skin from infectious agents.[1] In a preliminary study, the use of silver sulfadiazine–containing dressing was associated with a lower total severity of RID.[35] Similar findings were reported for silver nylon dressing[36,37] or for Mepilex Foam Lite dressing.[38]

Table 1. Topical approaches currently used for the prevention and treatment of RID.

Study	Study design	Setting	Patients (n)	Treatments	Main outcomes
Campbell, 1992[33]	RCT	Adjuvant RT of breast or chest	99	1. No washing 2. Washing with water 3. Washing with water and soap	Lower acute skin reaction in washing groups
Roy, 2001[34]	RCT	RT for breast cancer	99	1. No washing 2. Washing with water and soap	Moist desquamation in 33% of no washing and 14% of washing groups; higher scores for pain, itching, burning in no washing
Hemati, 2012[35]	RCT	RT for breast cancer	102	1. Silver sulfadiazine 1% three-times/day, for 5 weeks 2. Controls	Median total score of skin injury: • Group 1: 5.49 • Control: 7.21 in controls
Niazi, 2012[36]	RCT	Rectal or anal cancer	42	1. Silver clear nylon dressing 2. Standard skin care	Mean dermatitis score: • Group 1: 1.67 • Standard of care: 2.53
Aquino-Parsons, 2010[37]	RTC	Breast RT	196	1. Silver clear nylon dressing 2. Standard skin care	No difference in incidence and size of moist desquamation and skin toxicity score
Zhong, 2013[38]	RCT	Nasopharyngeal carcinoma patients with radiodermatitis	88	1. Mepilex Foam Lite dressing 2. Usual care	Healing time: • Group 1: 16 days • Group 2: 23 days
Haruna, 2017[40]	Meta-analysis	Breast cancer	845	1. Topical corticosteroids	Reduced incidence of wet desquamation in treated patients
Ho, 2018[41]	RCT	Breast cancer	124	1. 0.1% mometasone furoate 2. Eucerin original cream	Moist desquamation: • Group 1: 43.8% • Group 2: 66.7% Lower incidence of skin toxicity; later occurrence of grade 3 dermatitis
Ghasemi, 2019[46]	RCT	Breast cancer	70	1. Topical 1% atorvastatin 2. Placebo	Atorvastatin reduced swelling, itching, and pain
Wells, 2004[48]	RCT	Head and neck, breast or anorectal cancer	357	1. Aqueous cream 2. Sucralfate cream 3. No cream	No differences among groups in severity of skin reaction
Falkowski, 2011[49]	Open	Breast cancer	21	1% sucralfate lotion	No radiodermatitis prevention
Elliott, 2006[50]	Phase III RCT	Carcinoma of oral cavity, pharynx, or larynx	547	1. Prophylactic trolamine emulsion 2. Interventional trolamine emulsion 3. Institutional preference	No benefit of trolamine tor incidence of radiodermatitis or quality of life
Fenig, 2001[51]	RCT	Breast cancer	74	1. Biafine 2. Lipiderm 3. No treatment	No advantage in any group to gaps in RT, patient impression, and skin reaction
Gosselin, 2010[52]	RCT	Breast cancer	208	Trolamine cream *versus* placebo	No reduction of RT incidence

(Continued)

Table 1. (Continued)

Study	Study design	Setting	Patients (n)	Treatments	Main outcomes
Abbas, 2012[53]	Phase III	Head and neck cancer	30	1. Trolamine emulsion 2. Usual care	Grade 3 skin reaction in 20% of group 1 and 53% of group 2
Imai, 2014[90]	RCT	Head and neck cancer, chemoradiotherapy	40	1. p-Hydroxy-p-methyl butyrate/ arginine/glutamine supplementation 2. No supplement	No difference in incidence of G3 dermatitis
Kang, 2014[57]	Observational	Cancer patients receiving >50 Gy	1172	EGF-based cream	Incidence of radiodermatitis was 46.6%, 18.0%, 5.5%, and 0.9% from grade 1 to 4, respectively
Kouvaris, 2001[58]	Open study	Vulvar carcinoma	61	1. Steroid cream 2. Steroid cream + GM-CSF	Reduced score of skin reactions and duration of RT interruptions
Chan, 2014[79]	RCT	RT for cancer	174	1. Allantoin emulsion 2. Aqueous cream	Allantoin emulsion is less effective than an aqueous cream on radiodermatitis
Heggie, 2002[60]	RCT	Breast cancer	225	1. Aloe vera gel 2. Aqueous cream	Aqueous cream was better in reducing dry desquamation and pain
Geara, 2018[62]	Randomized, open-label study	Breast cancer	161	1. p-sitosterol ointment 2. Trolamine cream	No difference in grade 2 and 3 dermatitis
Pommier, 2004[64]	RCT	Breast carcinoma	254	1. Topical Calendula officinalis 2. Topical trolamine	Reduced incidence of grade 2 dermatitis in group 1
Schneider, 2015[65]	RCT	Head and neck cancer	51	1. Topical Calendula officinalis 2. Topical essential fatty acids	The incidence of grade 2 dermatitis was higher in group 2
Zhao, 2015[75]	Single-arm trial	Breast cancer	24	Epigallocatechin-3-gallate solution	Grade 2 dermatitis regression was observed in 2 patients
Zhu, 2016[76]	Single-arm trial	Breast cancer	49	Epigallocatechin-3-gallate solution	Reduced pain in 85% patients, burning in 89%, and itching in 87% of patients
Liguori, 1997[70]	RCT	Head and neck, breast or pelvic cancer	152	1. Hyaluronic acid cream 2. Placebo	Better global efficacy judgment by physician and patient for hyaluronic acid
Franco, 2014[72]	Single-arm observational study	Head and neck cancer	28	*Hypericum perforatum* and neem oil	Reduction of grade of radiodermatitis
Manas, 2015[80]	RCT	Chemoradiation in head and neck cancer and breast cancer	98	1. Topical lactokine 2. Topical urea lotion	2 weeks after chemoradiation; 67% of group 1 and 34% of group 2 were free of radiodermatitis
Cui, 2015[81]	RCT	Chemoradiation in nasopharyngeal carcinoma	96	1. Olive oil during and after CRT 2 Placebo	Less severe dermatitis in group 1

(Continued)

Table 1. (Continued)

Study	Study design	Setting	Patients (n)	Treatments	Main outcomes
Palatty, 2014[82]	Two-arm open-label trial	Head and neck cancer	50	1. Turmeric and sandal wood oil cream 2. Usual care oil	Reduced grade of radiodermatitis al all time points in group 1
Shariati, 2020[54]	Double-blind RCT	RT for breast cancer	48	1. Doxepin (5%) cream 2. Placebo	Reduction of occurrence of acute dermatitis (grade 2 or higher)
Robijns, 2018[39]	RCT	RT for breast cancer	120	1. Laser therapy 2. Placebo	Prevention of the development of acute dermatitis (grade 2 or higher)
Liao, 2019[43]	RCT	Radical RT in head and neck squamous cell carcinoma	41	1. Mometasone furoate cream 2. No medication	Prevention of acute dermatitis when the radiation dose is <6000 cGY
Chan, 2019[55]	Single-blind, randomised controlled, superiority trial	Radical RT in head and neck cancer	197	1. StrataXRT® 2. 10% Glycerine (Sorbolene cream)	Prevention and delay of the development of skin toxicit (grade 2 and 3)
Zenda, 2018[42]	Double-arm, double-blinded RC Phase III trial	Chemoradiotherapy for head and neck cancer	220	1. Topical steroid 2. Placebo	Not reported – ongoing

Note: CRT, chemoradiotherapy; GM-CSF, granulocyte–macrophage colony-stimulating factor; RCT, randomized controlled trial; RT, radiotherapy.

Laser therapy

Photobiomodulation therapy after the RT session twice a week was tested in breast cancer patients. The effectiveness of the treatment was evaluated by a quality-of-life questionnaire and results in a beneficial effect.[39]

Pharmaceuticals and biological agents

Topical corticosteroids are commonly prescribed for RID because of their ability to counteract the radiation-induced release of cytokines.[32] While the efficacy of this therapeutic strategy is established in breast cancer[40,41] and is currently under evaluation in head and neck cancer,[42,43] the use of topical corticosteroids is frequently associated with the onset of clinically relevant adverse events.[44] In particular, the prolonged use of steroids leads to skin thinning, which may be particularly contraindicated in this condition. Statins display some anti-inflammatory, immunomodulatory, antioxidant, metabolic, and antibacterial properties and can have some efficacy in the reduction of severity of skin disorders, such as psoriasis, dermatitis, uremic pruritus, and vitiligo.[45] In a preliminary experience, Ghasemi and colleagues investigated the topical use of atorvastatin.[46]

In topical formulation, sucralfate presents barrier abilities, antibacterial activity, anti-inflammatory effects, and angiogenesis-promoting capabilities.[47] However, sucralfate did not reduce the severity of RID or improve patient-reported symptoms.[48,49]

Trolamine is extensively used for the management of RID, as it is supposed to function as a non-steroidal anti-inflammatory molecule.[1] However, several RCTs did not show any advantage for trolamine over supportive care or even placebo in treating RD.[50–53] Doxepin cream has been recently shown to prevent dermatitis when applied after RT in breast cancer patients.[54]

Silicone-based agents *in vitro* have been shown to regulate fibrosis and wound healing, although with potential practical inconvenience due to non-perfect adherence to the skin when bathing and in men with facial hair. StrataXRT®, a silicone-based film-forming agent, was shown to be effective in delaying the development of skin toxicity.[55]

EGF stimulates the proliferation of human epidermal stem cells, fibroblasts, and keratinocytes, thus contributing to skin lesion healing.[56] Kang and colleagues suggested that topical EGF leads to a diminished incidence of toxicity when compared with historical data.[57]

Granulocyte–macrophage colony-stimulating factor (GM–CSF) promotes macrophage maturation and activity. When compared with patients receiving topical steroids alone, patients on topical steroids and GM-CSF-soaked gauze displayed reduced severity of RID and milder pain.[58]

Non-pharmaceutical agents

Several non-pharmaceutical agents have been proposed for the amelioration of RID. Here, we review the available topical treatments and one oral agent. The agents have been classified according to their main property. This does not exclude that one agent could present more than only one feature.

Anti-inflammatory agents

- Aloe vera is an anti-inflammatory herbal therapy endowed with protective and healing abilities.[59] However, despite these promising characteristics, aloe vera does not reduce the severity of RID.[60]
- Beta-sitosterol is a herbal formulation presenting antibacterial, analgesic, and anti-inflammatory effects.[61] In a recent clinical trial, beta-sitosterol and trolamine were not associated with relevant improvements in RID, although the incidence of severe pruritus and local pain were both significantly reduced with beta-sitosterol.[62]
- *Calendula officinalis* has anti-inflammatory, antibacterial, antifungal, antioxidant, and angiogenic abilities.[63] In an RCT, calendula significantly lowered the frequency of grade ≥2 acute dermatitis compared with trolamine (41 *versus* 63%, $p<0.001$). Moreover, patients assigned to calendula required fewer interruptions in RT and reported milder pain.[64] These findings were confirmed in a more recent pilot randomized trial.[65]
- Hyaluronic acid (HA) is widely used in wound dressings, skin substitute products, and other applications in the field of regenerative medicine and dermatology.[66,67] HA is used in high-molecular weight and low-molecular weight forms, and the use of conjugated high- and low-molecular weight HA can further increase the efficacy of this compound, in a synergic fashion.[68] *In vitro*, HA protected fibroblasts from radiation damage,[69] and in a double-blind RCT, HA was able to reduce the incidence of severe RID in 152 patients undergoing RT for head and neck, breast, or pelvic carcinomas.[70] Recent evidence also supports the clinical use of HA for topical administration in patients with inflammatory conditions at the level of mucosa.[71]
- In a pilot study, Franco and colleagues prospectively evaluated the role of *Hypericum perforatum* and neem oil in the treatment of acute skin toxicity.[72] This approach was preliminary and suggested to be safe and active in the management of this condition.
- Glutamine has been proposed to prevent oral RID and mucositis. However, a study evaluating the efficacy of oral glutamine showed no significant effect on the severity of oral mucositis.[73]

Antioxidant agents

- Catechins, in particular epigallocatechin-3-gallate (EGCG), present antioxidant activities that may promote healing of skin damage caused by exposure to ultraviolet light.[74] In a phase I/II clinical trial, topical EGCG showed several beneficial effects.[75,76]
- Vitamins have also been tested in this setting. Ascorbic acid is endowed with powerful antioxidant and free radical-scavenging abilities. These characteristics led Halperin and colleagues to study the possible protective role of ascorbic acid in RID, but their study failed to demonstrate any benefit of topical ascorbic acid in this setting.[77] Pantothenic acid (vitamin B5) has a central role in metabolism, and is essential for the integrity of normal skin. However, when compared with no treatment, a topical cream with pantothenic acid failed to show an enhanced protective effect against RID.[78]
- Topical preparations that contain comfrey extract, which comprises allantoin, may have some applications in the treatment of skin irritation. Indeed, in a double-blind trial, patients assigned to the allantoin-containing cream had a lower severity of pain and itching at week 3 compared with those on aqueous cream.[79]
- Lactokine is a protein derived from milk. In a pilot study, topical administration of a lactokine-containing product was effective in preventing and reducing the grade of RID in head and neck and breast cancer patients.[80]
- In an RCT on 94 patients with head and neck cancer, the acute RID that resulted was decreased in intensity with the application of olive oil.[81] In another small randomized study on 50 patients, a cream containing turmeric and sandal wood oil was able to prevent the onset of RID, but the results require further validation in larger double-blind trials.[82]

From bench to bedside: how to improve treatment of RID

RID has a major impact on quality of life of cancer patients and may interfere with oncologic therapies, thus reducing their effect.[4] In particular, pain is perceived as among the most severe symptoms associated with RID,[7] and also other symptoms experienced by patients – for example, itching and burning – are bothersome for patients.

From a basic research perspective, an improved understanding of the mechanisms of radiation-induced damage of the skin will lead to the opportunity to better schedule both preventive and curative strategies. Moreover, a large effort is needed to find predictive factors for the onset and severity of RID, also at a genomic level.[2]

It is of utmost importance to conduct proper epidemiological studies and nationwide surveys, with the aim to capture a clearer picture of incidence of RID and treatment approaches in different centers (e.g. primary *versus* referral centers).

Box 1. Practical tips for the clinical management of RID.

- Wash irradiated skin with lukewarm water and a mild pH, neutral or non-alkaline, soap daily
- Shave with a sharp, disinfected wet razor or with non-traumatizing electric razor
- Wear loose-fitting clothes in order to prevent friction injuries over the irradiated area
- Avoid extreme temperatures and sun exposure
- Avoid the use of metallic-based topical products, perfumes, and the use of tapes and adhesives
- Choose a proper topical product for each patient in order to keep the skin hydrated
- Any topical product should not be applied over the irradiated skin from 1 to 4 hours before the daily treatment
- Consider dressings and advanced medications in case of wet desquamation
- Prevent superinfections
- Consider topical or systemic antimicrobials in case of infection
- In case of grade 3 RID, every effort should be made to try not to interrupt RT
- In case of grade 4 RID, consider discontinuation of RT

RID, radiation-induced dermatitis; RT, radiation therapy.

At present, there is no standard treatment for RID, and a more rational approach to the therapy of this condition has been advocated.[4] Properly designed prospective studies, possibly RCTs, investigating RID should be conducted to collect high-level evidence on this topic, which is currently lacking. These studies should contemplate PROs and quality-of-life measures as main outcome measures. An important pitfall is the lack of a reliable objective tool to measure RID. Methods used and reported in the literature are reflectance spectrophotometry, a non-invasive technique aimed at measuring cellular pigments, and trans-epidermal water loss (TEWL) measurement, to analyze the epidermal barrier function.[83,84]

To overcome current doubts and help clinicians in managing patients with RID, here we provide some practical tips that can be easily suggested to patients (Box 1).

The ideal therapy for RID should present a number of characteristics and be based upon a rational selection of components. First, cancer patients are in almost all cases polymedicated, and receiving a number of treatments associated with bothersome adverse events. Hence, a topical product for the therapy of RID, with limited risk of systemic adsorption and drug–drug interaction, may be preferred, in line with previous recommendations in the dermatological setting.[30] Moreover, the product should address the complex array of manifestations of RID, and hence should be characterized by the combinations of a few selected active principles with different mechanisms of actions or targets and multiple clinical activities to counteract such diverse symptoms. Agents able to prevent the earlier events, such as production of free oxygen radicals or inflammatory mediators, should be combined with molecules that could stimulate healing and regeneration. In particular, as pain is recognized to be the most bothersome symptom associated with RID, particular attention should be paid to its management. The investigation in this setting of molecules with an established action on localized pain (e.g. carnitine[85,86]) can be of the highest interest.

The need of multiple actions should be, however, weighed against the need for limiting risk of adverse events and drug–drug interactions, and therefore the minimum possible number of components should be included. Furthermore, the formulation should be carefully selected: for instance, an oily phase may block the penetration of the RT beam. Hence, formulations without an oily phase, such as gels, may be preferred over those containing this (e.g. creams).

Proper selection of vehicle has also a major role, as it may influence the penetration into the different skin layers, and thereafter the cell targets eventually reached. Liposome formulations are able to uniformly penetrate the horny layer leading to a 4–14-times higher local concentration of active substances compared with conventional emulsions.[87] Moreover, beyond their role as carriers, liposomes can be considered as active agents, given their richness in phospholipids and omega fatty acids, for the treatment of dry, scaly, and flaky skin.[87] In an *in vitro* study, an ascorbate phosphatidylcholine liposome was shown to overcome the stratum corneum and deliver the active agent into the dermis to prevent photodamage.[88] These findings were mirrored in another experimental study.[89]

Hence, a topical product containing rationally selected components able to address pain, skin damage, and the other bothersome symptoms of RID – delivered by proper vehicle – ensuring, at the same time, optimal chemo-physical properties would be of the highest interest in the current treatment scenario for RID. Such a compound may be used also in the preventive setting, in line with recent suggestions,[4] in order to limit the onset of RID, improve the quality of life, and reduce the risk of RT interruptions.

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