A novel treatment to delay the onset of radiotherapy-induced skin reaction

KEY WORDS
- Emollient therapy
- Hydroactive colloid gel
- Prophylaxis
- Radiotherapy-induced skin reaction (RISR)

In this article, the author discusses current topical treatments used in the treatment of radiotherapy-induced skin reaction (RISR) and discusses an alternative, Flamigel® (Flen Health UK). A moderate to severe radiotherapy-induced skin reaction may necessitate a break in treatment; this novel product can reduce the onset and severity of RISR, thus potentially ameliorating treatment breaks (Harris et al, 2011; Censabella et al, 2017). The author of this article experienced a mild RISR during radiotherapy treatment that developed at about day 7. While this did not delay treatment, the effects could at times be difficult to manage. The mild discomfort was tolerable, but the worst symptom was the itching.

While the pathology of wounds such as pressure ulcers, leg ulcers and diabetic foot ulcers is well researched and documented, this is less true of radiotherapy-induced skin reaction (RISR).

WHAT IS RADIOTHERAPY-INDUCED SKIN REACTION?

While radiotherapy treatment is vital for tumour management, it can cause severe skin reaction. All patients receiving external radiotherapy beam therapy (EBRT) are at risk of developing a reaction; the incidence is said to range from 85% (Robson and Cooper, 2009; Salvo et al, 2010) to 95% (McQuestion, 2011).

Due to the appearance of RISR, it is easy to mistake for a burn injury; however, as Trueman (2013) states, the mechanisms, extent, duration and trajectory of injury is different (*Table 1*).

Table 1. Differences between RISR and burn injury

Type of injury/ Presentation	Cause	Presentation	Physiological progression
Burn	Trauma from hot liquid, fire, ice or chemicals	Immediate	Outer layers of skin downwards
RISR	Absorption of ionising radiation	Delayed/ Cumulative	Basal cell upwards

External radiotherapy beam therapy destroys the cancer cells in the treatment area by either directly damaging cancer cell DNA, or by creating charged particles (free radicals) which damage DNA, thus causing cells to stop growing or die. The radiation damages the basal layer of the epidermis, and the subsequent imbalance between the normal production of cells in this layer and the destruction of cells at the skin surface causes radiation induced skin reaction (Trueman, 2011).

Radiation is delivered in small doses (called fractions), which in theory allows time for healthy cells to recover between treatments; however, because each fraction damages cells, skin damage is cumulative. This damage is assessed using tools such as the Radiation-Induced Skin Reaction Assessment Scale (RIRAS) (Noble-Adams, 1999), or the more commonly used Radiotherapy Oncology Group (RTOG) assessment tool (Cox et al, 1995; Glean, 2000) (*Table 2*). This development of skin damage can be summarised thus:

- 10–14 days from first dose, damaged basal cells migrate to the skin surface and erythema develops — RTOG 2
- As more fractions are given, further skin damage occurs; new cells reproduce before old dead cells shed leading to dry desquamation — RTOG 2a

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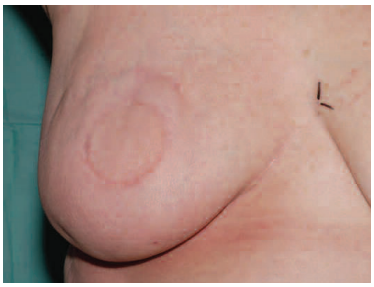
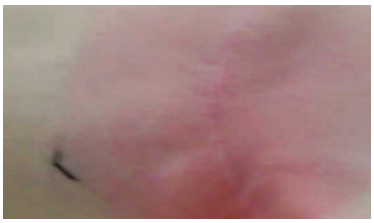
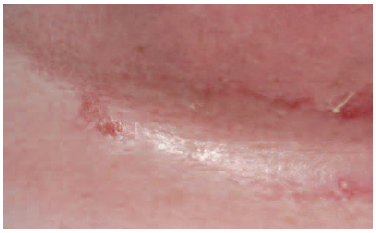
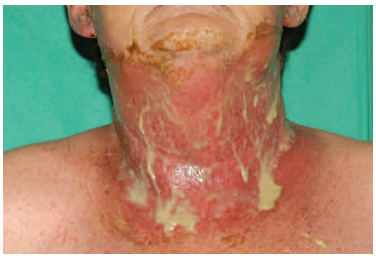
Table 2. RTOG assessment tool (Glean et al, 2000)

Score	Description	Presentation
RTOG 0	No visible change	Immediate
RTOG 1	Faint or dull erythema	
RTOG 2a	Tender or bright erythema with/ without dry desquamation	
RTOG 2b	Patchy moist desquamation; moderate oedema	
RTOG 3	Confluent moist desquamation; pitting oedema	

- Where no new cells replace dead cells, moist desquamation occurs — often called radiotherapy-induced moist desquamation (RIMD) — RTOG 2b — RTOG 3.

Because RISR is a result of cumulative radiation doses, symptoms do not usually show until 1–4 weeks after the start of treatment. As reaction can worsen over time, treatment (radiotherapy) may have to be postponed until adequate healing has occurred. Such delays can have a detrimental effect on treatment outcome (Harris et al, 2011).

Skin damage can present between 10 and 14 days post-treatment, when damaged basal cells migrate to the skin surface (NHS Quality Improvement Scotland, 2010). Thus, management of RISR tends to be shared by radiographers, oncology nursing staff and primary care nursing staff, potentially compromising care (Bostock, 2016). A simple, anonymous survey of 105 community nurses was undertaken via the *Journal of Community Nursing* website to determine their knowledge of RISR (Flen Health, data on file). As this survey was purely designed to capture current knowledge, questions pertaining to follow-up after referral and what drove their referral choice were not asked. Results demonstrated that:

- 74.3% of respondents saw patients with RISR
- 21.9% treated the patient directly
- Referrals were made to: GPs (33.3%), radiotherapy centres (18%) and other specialists, such as tissue viability or dermatology nurses (5.7%)
- Interestingly, 20.9% referred to all of the above.

Forty-one percent of respondents advised patients about self-management (such as bathing and general hygiene), 23.8% used emollients, 15.2% used dressings and 20% provided pain relief. However, interventions such as corticosteroid cream, aqueous cream, Intrasite gel mixed with diamorphine on dressings and 'non-adherent dressings for burns' were used, which confirm that management of RISR is inconsistent and in some cases, inappropriate (Tsang and Guy, 2010, Medicines and Healthcare Regulatory Agency [MHRA], 2013). Indeed, aqueous cream is still frequently used, yet has been shown to be harmful (Tsang and Guy, 2010; Danby et al, 2011). The MHRA have expressed concerns about its use as an emollient (MHRA, 2016). Its key advice is that:

- Aqueous cream contains sodium lauryl sulphate (SLS) that may cause local skin reaction (for example, stinging and contact dermatitis), particularly in children with atopic eczema. Other ingredients such as preservatives may also contribute to skin reaction
- During an eczema treatment consultation, healthcare professionals should inform patients that skin irritation (such as burning, stinging, itching or redness) may occur if aqueous cream is used as a leave-on emollient, often within 20 minutes of application.

- If a patient has skin irritation (burning, stinging, itching or redness) after the use of aqueous cream, they should discontinue treatment, and talk to their healthcare professional who will be able to advise on suitable alternative treatments.

Aqueous cream can be used as a soap substitute but should not be left on the skin as an emollient.

RISK FACTORS FOR RISR

It has been postulated that a number of intrinsic and extrinsic factors contribute to the risk of RISR (Trueman et al, 2011; Censabella et al, 2014).

Intrinsic factors:

- Age
- Comorbidities/medication
- Long-term UV exposure/ethnicity
- Obesity
- Wound/skin infection
- Location of treatment — breast and areas of skin fold are more susceptible as higher doses of radiation reach the skin folds (Vuong et al 2004).

Extrinsic factors:

- Total dose of radiation; high doses to large treatment fields also increases the risk of skin damage (Harris et al, 2011)
- Irritants such as deodorant, perfume, talcum powder, friction and heat during treatment.

CURRENT TREATMENT

According to Trueman et al (2013), the goals of RISR management are:

- To maintain skin hydration and integrity
- To minimise further exacerbation of the reaction and to prevent trauma and infection
- To reduce pain and maintain patient comfort
- To maintain a moist wound healing environment where skin is broken.

In 2014, the Society of Radiographers (SoR) undertook a survey of current RISR treatments (SoR, 2014), which demonstrated that despite the publication of best practice guidelines for radiotherapy skin care in 2011, RISR care in UK radiotherapy departments varies, and that within the published research no one topical application or medical intervention is deemed superior over another. The survey also found that aqueous cream was issued in radiotherapy departments for prophylaxis or to alleviate erythema (81% and 65% of UK departments respectively), despite recent studies that have indicated that aqueous cream containing sodium lauryl sulphate may:

- Compromise skin integrity (Tsang and Guy, 2010; Patel et al, 2013)
- Be an irritant when used as a leave-on emollient (Tsang and Guy, 2010; Patel et al, 2013; MHRA, 2013)
- Cause thinning of the outermost layer of the skin and increased skin water loss when used as an emollient in adults, both with and without eczema (Tsang and Guy, 2010; Danby et al, 2011).

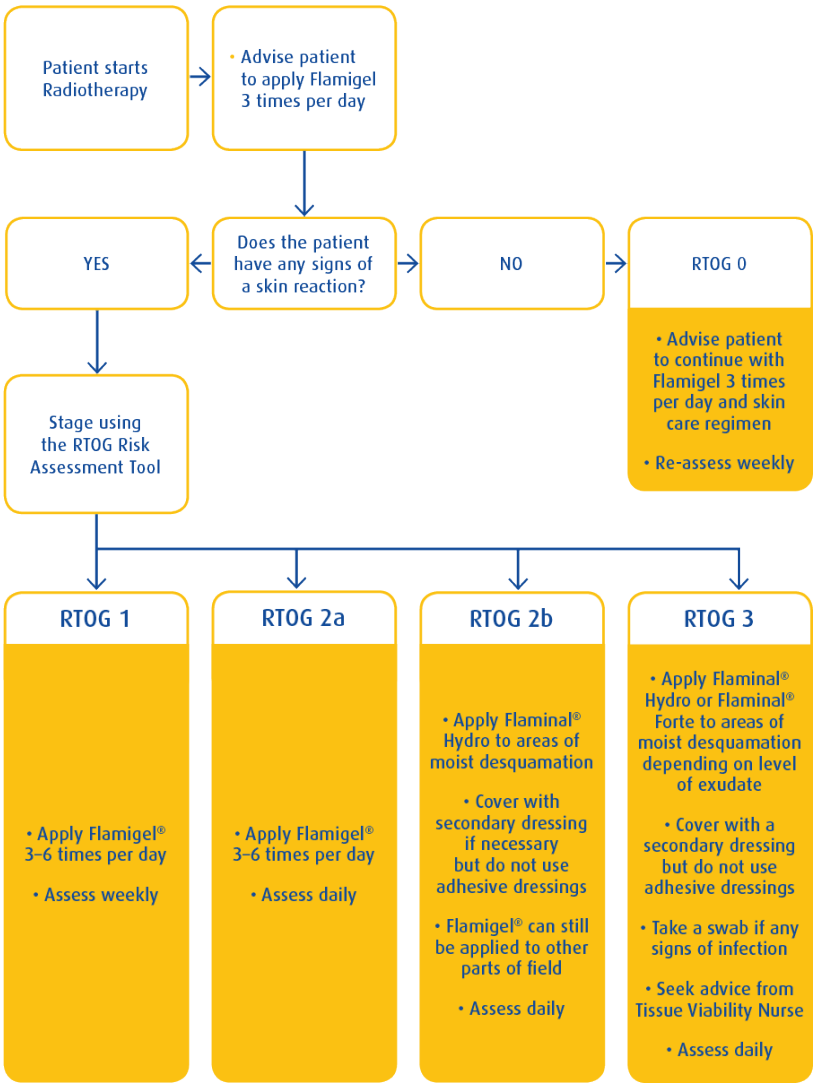
The SoR therefore recommended that a sodium lauryl sulphate free moisturiser for prevention and/or management of RTOG 0–2a is used. Despite this recommendation, aqueous cream is still widely in use outside of radiotherapy departments, as are other products such as prophylactic dressings (Diggelmann et al, 2010; Bostock, 2016) topical steroids, dexpanthenol cream (Censebella et al, 2014), and aloe vera (Hoopfer et al, 2014).

FUTURE MANAGEMENT OF RISR

Given that RISR can be painful for the patient and can delay or halt radiotherapy, it would appear evident that delaying the onset of RISR is as important as its management. However, little evidence exists as to which prophylactic approach to use. According to an expert consensus: *"... a hydroactive colloid gel ... which donates and absorbs moisture according to the wound's properties, can generally be recommended in the management of minor skin wounds because it can be used on dry and exuding wounds."* (Ferrera-Alves et al, 2009). Hydroactive colloid gels regulate moisture in the wound (Korting et al, 2011) thereby reducing potential for skin irritation and/or damage. In addition, their cooling effect can reduce pain/burning sensations (Ferreira Alves et al, 2009) and alleviate irritation (Van den Plas et al, 2009; McQuestion, 2011).

Flamigel® (Flen Health, UK) is a new topical application formulated to reduce incidence and delay the onset of RISR and ameliorate symptoms, thus fitting the criteria outlined by Ferrera-Alves et al (2009). It is a hydroactive colloid gel that forms a protective film on the epidermis. This gel's protective barrier allows gaseous exchange while capturing epidermal water thereby acting

Figure 1. Flamigel treatment pathway



as a moisturiser, and it absorbs excess moisture from a wet wound. The gel comprises purified water, arginine (an amino acid essential for cell division, which facilitates the synthesis of collagen), branch-chain fatty acid, and a polymer in an active and inactive state (Flen Health, 2016). The action of this polymer is determined by the level of moisture in the skin: in dry conditions, the polymer donates moisture (hydrogel effect) and in high moisture levels the inactivated polymer is activated and absorbs excess moisture (hydrocolloid effect). This maintains and optimum moisture balance in the skin. The absorption properties are based on those of hydrocolloid dressings, which are known to absorb liquid in the presence of wound fluid. Arginine is added to the formulation to partially neutralise the acid polyacrylate polymer, allowing hydration of the dry wound (hydrogel effect). The non-neutralised part of the polyacrylate polymer is naturally neutralised by proteins in wound exudate, thereby absorbing the excess exudate — the more exudate, the higher the concentration of activator proteins, the more readily Flamigel® will absorb moisture.

Aspects of absorbency were tested according to the requirements of EN standards 13726-1:2002 (Surgical Materials Testing Laboratory, 2011).

Figure 1 outlines the treatment protocol for its use. The skin care regimen included in the pathway will be determined by local guidelines.

A retrospective crossover study undertaken by Censabella et al (2014) compared the efficacy of two topical agents, dexpanthenol cream (Bepanthol® Cream, Bayer AG, Leverkusen, Germany, [often used for nappy rash]) and a hydrocolloid gel (Flamigel®) in managing RIMD in breast cancer patients. Data from two cohorts of patients (n=483) undergoing radiotherapy for breast cancer was retrospectively analysed, although how these were allocated to the cohorts is not shown. The first (n=267) received dexpanthenol cream for the duration of their radiotherapy (3 times a day, every day). This was part of standard skin care regimen. The second cohort (n=216) used dexpanthenol cream for the first 11–14 days of treatment, then changed to Flamigel® at day 11–14 (that is, after a received cumulative radiation dose of 26 Gy). The rationale for the two-week change was that most RISRs occur at this time in treatment. Both cohorts received the same radiation treatment (technique, total dose, equipment). As breast size is a risk factor for RISR — greater radiation changes are related to greater dose inhomogeneity in women with large breasts (Moody et al, 1994; Porock et al, 1998), patients were categorised according to the distance between the two entrance points of the beams (< or ≥ 20 cm). The presence of RIMD was recorded by the oncology nurses caring for the patients as the first signs appeared. Two-sample proportion tests were performed to compare the efficacy of the two treatments.

Results showed that there were significantly more patients with large breast size in the

hydroactive gel than in the dexpanthenol group. The overall incidence of moist desquamation was significantly greater in patients with large than with small breast size (32% versus 13%, respectively (p<.0001). However, the overall incidence of moist desquamation was significantly lower in those who had applied the dexpanthenol cream and hydroactive colloid gel, than in those patients applying the dexpanthenol cream throughout (16% versus 32%). Furthermore, RIMD occurred significantly later with the hydroactivecolloid gel than with the dexpanthenol cream.

Censabella et al (2017) undertook a further study that aimed to determine if Flamigel® applied from day 1 of radiotherapy treatment could prevent RIMD in breast cancer patients (preventative group n=258) as opposed to standard care, Dexapanthenol. Patients were included if they were to receive 25 daily fractions of 2 Gy to the whole breast (five times/week) followed by an 8-fraction boost to the tumour bed, for a total dose of 66 Gy. Exclusion criteria were previous irradiation to the same breast, metastatic disease, use of bolus material, and concomitant chemotherapy (adjuvant or neoadjuvant chemotherapy, hormone therapy and/or trastuzumab was allowed). The study protocol was approved by the local Medical Ethics Committee.

A group of 222 patients met these criteria and were included after signed informed consent was obtained. They were required to apply the hydroactive colloid gel (Flamigel) to the irradiated area from start to end of radiotherapy (hereafter referred to as the Preventive Hydrogel group). This group was compared with two groups of matched historical controls from the previous study (Censabella et al, 2014), enrolled with the same eligibility criteria, hence undergoing the same radiotherapy regimen post-lumpectomy: the first group applied a 5% dexpanthenol cream (Bepanthol) throughout their radiotherapy (Dexpanthenol group, n=136), the second one applied the dexpanthenol cream from the start of radiation therapy then, after 11–14 days, replaced it with the hydroactive colloid gel until completion of therapy (Curative Hydrogel group, n=100). To note, originally, the two historical control groups had equivalent sample size but half of these patients received the first 25 fractions with 4-MV photons beams (they were only 20% in the Preventive Hydrogel group). As this was a somewhat outdated technique and a potential bias, we decided to exclude these patients, what led to this rather unbalanced design. Patients in this study and the previous comparator studies received the same skin care regimen during radiotherapy; patients were asked to follow general skin care recommendations (e.g. gently washing with mild soap or non-soap cleansers; patting dry with a soft towel instead of rubbing; wearing soft, loose clothing) and were instructed to apply a dollop of product three times a day. Dry/patchy moist desquamation was treated by applying self-adhesive silicone foam as secondary dressing (Mepilex® or Mepilex Lite®, Mölnlycke Health Care, Gothenburg, Sweden). In case of confluent moist esquamation, patients stopped using either the dexpanthenol cream or the hydroactive colloid gel and other wound care products more appropriate to moderately to heavily exuding wounds were applied.

Results were compared with the 2014 study groups (dexpanthenol only and dexpanthenol until day 11–14, then Flamigel®) and show that overall, there was a 5-fold reduction in RIMD with the Flamigel® preventative group compared with the group who received dexpanthenol alone (7% versus 35%) (*Figure 2*). Moreover, patients in the preventative group developed RIMD significantly later than patients in the dexpanthenol, with greater RIMD-free survival probability (*Figure 3*). These results confirm those of the previous study (Censabella et al, 2014); applying the hydroactive colloid gel

Figure 2. Percentage of patients with moist desquamation

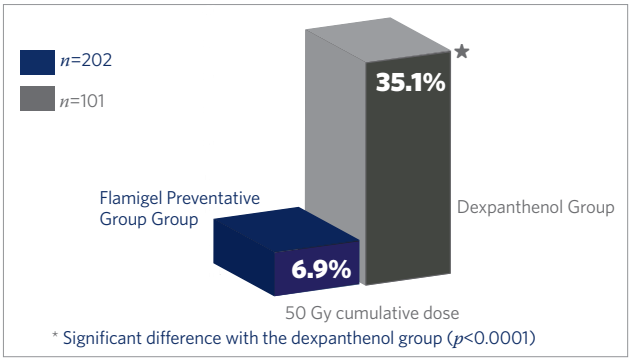
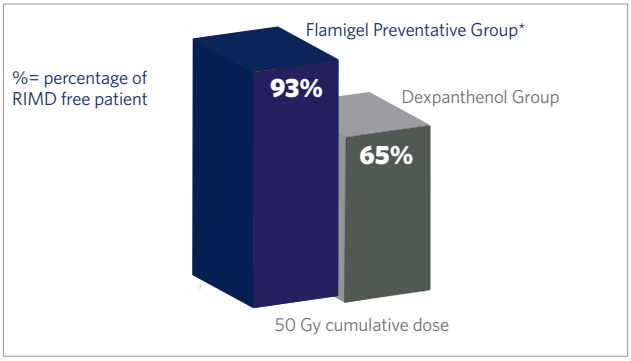


Figure 3. Difference in onset of RIMD change



from the start of radiotherapy rather than dexpanthenol led to both a delayed onset and reduced incidence of RIMD.

A recent evaluation of the product undertaken by 43 UK healthcare practitioners using Flamigel® for RISR sought to determine if it reduced erythema and pain, changed the nature of pain, if desquamation developed during use, and if it alleviated pruritus (where present). Results showed that:

- 45% felt it reduced erythema (100% response)
- 92% stated that it reduced pain in inflammed areas (84% response)
- 69% noted that it reduced pain over the course of treatment, 31% noted no change (88% response)
- Flamigel® prevented the occurrence of RIMD in 90% of patients (93% response)
- Pruritus improved in 68%, remained the same in 32% (86% response).

It should be noted that at the time of the evaluation, 74% of the patients already had RTOG 1 skin damage, so damage to the basal layer had occurred and erythema was present. Use of the product lowered the intensity and pain associated with the existing RISR and prevented RIMD.

DISCUSSION

Radiotherapy-induced skin reaction particularly at moist desquamation stage, can be both painful and distressing for patients (McBride et al, 2008; Gosselin et al, 2010). Depending on the severity of the RISR, radiotherapy may be interrupted until it has resolved which can negatively influence treatment outcome (Bese et al, 2007). Delaying the onset of moist desquamation is critically important in order to allow treatment to continue without interruption, as evidenced by the Censabella et al (2017) retrospective study, which demonstrated during the first 25 fractions of radiotherapy (i.e. with data censored at 50 Gy), the incidence of RIMD was overall lower in the Preventive Hydrogel group than in the Dexpanthenol and the Curative Hydrogel group (6.9% versus 35.1% and 12.6% [95% CIs: 4.2e11.3%, 27.5e43.6%, and 7.2e21.2%, respectively], p <0.0001.

Salvo et al (2010) undertook a literature review of 33 trials that investigated products for RISR prophylaxis and six that explored the management of acute radiation dermatitis. They concluded that while the studies evaluated a range of products (topical corticosteroids, nonsteroidal topical agents, aloe vera, sucralphate cream, washing with soap and water) used for the prevention of acute radiation-induced skin reaction, none of the results "support a general consensus on a superior product that should be used in this setting" (Salvo et al, 2010). Similarly, none of the treatments for RISR were shown to be superior, although the studies were of poor quality (Salvo et al, 2010).

Dressings have been used both for prophylactic prevention and management of RISR. However, when used for the management of RISR or RIMD, they may require frequent changing, and no one dressing works for all stages of healing. In addition, dressings can be costly and may even cause more damage to fragile skin (Bostock, 2016). However, many studies (Ferrera-Alves et al, 2009; Van den Plas et al, 2009; Korting et al, 2011; McQuestion, 2011) have demonstrated that hydrocolloid gels can be used on both dry and exuding wounds due to their moisturising and absorptive effects. This makes them ideal for use in patients who are undergoing ERBT as RISR is almost inevitable; such patients require a product that can delay the onset of RISR such as moist desquamation and reduce its incidence. Flamigel® can be covered by a dressing if the skin is particularly irritated.

CONCLUSION

The studies reported here suggest applying Flamigel® from day 1 of radiotherapy rather than an alternative product such as dexpanthenol, delays the onset and reduces the incidence of RISR. Patients can have a greater cumulative radiation dose before the onset of MD. While no economic evaluation has been undertaken to date, logic suggests that prevention and/or faster management of RISR will save money. WUK

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