European Journal of Oncology Nursing 29 (2017) 1–7

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

journal homepage: www.elsevier.com/locate/ejon

Efficacy of a hydroactive colloid gel versus historical controls for the prevention of radiotherapy-induced moist desquamation in breast cancer patients

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ARTICLE INFO

Article history:
Received 30 May 2016
Received in revised form
27 March 2017
Accepted 13 April 2017

Keywords:
Breast cancer
Dexpanthenol
Hydroactive colloid gel
Hydrocolloid
Hydrogel
Moist desquamation
Radiation dermatitis
Radiodermatitis
Radiotherapy-induced skin reactions
Wound healing

ABSTRACT

Purpose: Radiotherapy-induced moist desquamation (RIMD) is a complication that can affect patients' quality of life and jeopardize radiotherapy outcomes. The curative use of a hydroactive colloid gel has previously been shown effective in the management of RIMD in breast cancer patients. This study aimed at investigating the efficacy of this same gel but in the *prevention* of RIMD.
Methods: A group of breast cancer patients who applied the hydroactive gel from start to end of post-lumpectomy radiotherapy (Preventive Hydrogel group) were compared with two groups of matched historical controls: a group applying a dexpanthenol cream throughout their therapy and a group applying first the dexpanthenol cream then, after 11–14 fractions of radiotherapy, the hydroactive gel (Curative Hydrogel group). All patients received identical fractionation regimen. The clinical outcomes were the incidence and time to onset of RIMD.
Key results: After 25 fractions of radiotherapy (50 Gy), patients in the Preventive Hydrogel group (N = 202) developed RIMD significantly less frequently and later than patients in the Dexpanthenol group (N = 131; incidence = 7% vs 35% respectively, odds ratios = 7.27; probability of RIMD-free survival after 50 Gy = 0.88 vs 0.62). There were no significant differences between the Preventive and the Curative Hydrogel group (N = 87).
Conclusions: These findings confirm our previous results: applying the hydroactive colloid gel, rather than dexpanthenol, delayed the onset and reduced the incidence of RIMD in breast cancer patients. However, applying the hydrogel preventively offered no statistically significant advantages over applying it curatively.

1. Introduction

About 70–80% of breast cancer patients will undergo radiation therapy at some point as part of their cancer treatment (Barton et al., 2014). Of these, up to 90–95% will develop, to some extent, skin reactions during or shortly after the completion of radiotherapy (Sundaresan et al., 2015; The FAST Trialists group, 2011). Acute skin reactions, or radiation dermatitis, occur as a consequence of ionizing radiation, as used in radiotherapy, that damages the mitosis of skin cells (hampering their regeneration and thereby, damaging the integrity of the upper layer of the skin) and alters the healing process (leading to structural, histologic, and vasculature changes of the skin and underlying connective tissue). Ultimately, irradiation leads to inflammation, decreased functional stem cells, altered endothelial cells, and cell apoptosis and necrosis. Moreover, irradiation has a cumulative effect on the skin, so that skin reactions aggravate during the course of radiotherapy (Denham and Hauer-Jensen, 2002; Gieringer et al., 2011). The risk of developing radiation dermatitis and its severity depend on multiple factors,

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http://dx.doi.org/10.1016/j.ejon.2017.04.003
1462-3889/

including the location of the irradiated zone, with body regions containing skin folds (such as the groin or the breasts) being at higher risk. The total irradiation dose and the fractionation regimen (i.e., the dose delivered per fraction), the volume of tissue that is irradiated, the use of other concurrent cancer therapies (e.g., concomitant chemotherapy increases the risk, Fiets et al., 2003), or larger breast size constitute other risk factors for radiation dermatitis (e.g., Fowble et al., 2016; Hymes et al., 2006; Kraus-Tiefenbacher et al., 2012).

The severity of radiation dermatitis is graded on a continuum ranging from dryness or red rashes and dry desquamation to the more severe moist desquamation (O'Donovan et al., 2015). Radiotherapy-induced moist desquamation (RIMD), characterised by sloughing skin blisters filled with serous exudate, typically occurs after four to five weeks of radiotherapy (after a cumulative radiation dose of 40 Gray [Gy]), peaks shortly after the end of therapy, and heals within three months after completion of therapy (Hymes et al., 2006). Despite this gradual (natural) healing and its relatively low incidence (10–15%, Wells and MacBride, 2003), RIMD can be particularly painful and distressing for patients, potentially necessitating an interruption of radiation treatment (Kirova et al., 2011; Pommier et al., 2004) and in rare cases resulting in local infection (Salvo et al., 2010), all of which can negatively influence treatment outcome (Bese et al., 2007).

Over the years a large variety of products have been used to prevent and manage RIMD (e.g., calendula, gentian violet, hyaluronic acid, lanolin gauze dressings, sulfadiazine, or silicone dressings, see for example D'Haese et al., 2005; Harris et al., 2012; O'Donovan et al., 2015; Yuen and Arron, 2016). Yet there is insufficient (and even conflicting) evidence as to the efficacy of these products and many reviews and meta-analyses highlight the lack of strong, consistent scientific evidence regarding which product to use or when to use it for optimal results (Feight et al., 2011; The Society and College of Radiographers, 2015; Wong et al., 2013).

In a previous study (Censabella et al., 2014), we retrospectively compared the efficacy of a 5% dexpanthenol cream with a hydroactive colloid gel that combines the moisturising and absorbing properties of hydrocolloids and hydrogels. Dexpanthenol, one of the agents commonly used in radiotherapy centres (O'Donovan et al., 2015), is an alcohol analogue of pantothenic acid, a provitamin known to accelerate and improve wound healing by promoting epithelial formation and regeneration. It acts like a moisturizer when used topically and reduces itching and inflammation (Ebner et al., 2002), though evidence supporting its effectiveness in preventing radiotherapy-induced skin reactions remains insufficient (Wong et al., 2013). The hydroactive colloid gel contains purified water, arginine (an amino acid essential for cell division), branched-chain fatty acid, and a polymer in an active and an inactive state. The action of this polymer is determined by the wound itself: in dry wounds, the active polymer donates moisture ("hydrogel" effect) and, in exuding wounds, the inactive polymer is activated by the exudate and then absorbs it ("hydrocolloid" effect), maintaining an optimal moist environment that improves wound healing (Field and Kerstein, 1994). We found a significantly lower incidence and a delayed time to onset of RIMD in breast cancer patients who applied the dexpanthenol cream then, after 11–14 days, replaced it with the hydroactive colloid gel, than in those patients applying the dexpanthenol cream throughout the radiotherapy (16% vs 32%). Further, RIMD occurred significantly later with the hydroactive colloid gel than with the dexpanthenol cream.

The aim of the present study was to investigate the efficacy of this same hydroactive colloid gel in the *prevention* of RIMD, with the hypothesis that using this agent preventively would be even more beneficial with respect to incidence and onset time of RIMD. Therefore, we asked a group of breast cancer patients to apply this hydroactive colloid gel throughout their radiotherapy and compared them with these two previous groups of patients serving as historical controls.

2. Methods

2.1. Participants

All women who underwent conservative surgery for breast cancer and were further scheduled for conventional radiotherapy at the Limburg Oncologic Centre (Hasselt, Belgium) between June 2012 and July 2013 were screened for eligibility. 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 neo-adjuvant 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®, Flen Pharma NV, Kontich, Belgium) 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® Cream, Bayer AG, Leverkusen, Germany) 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.

2.2. Radiation therapy and skin care

Radiotherapy was planned using the Eclipse™ treatment planning system (version 10.0, Varian Medical System, Palo Alto, CA) and treatment was delivered by 6 MV photon beams. Segmented fields were used where required in order to reduce hot spots. The second series of boost was delivered using either photon (6–18 MV) or electron beams (9–15 MeV).

During radiotherapy, skin care protocol remained the same for all three groups. 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 a self-adhesive silicone foam as secondary dressing (Mepilex® or Mepilex Lite®, Mölnlycke Health Care, Gothenburg, Sweden). In case of confluent moist desquamation, 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.