ISSN 2035-0686
Official Journal of the ISPLAD

Journal of Plastic Dermatology

International-Italian Society of Plastic-Aesthetic and Oncologic Dermatology

ISPLAD

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Summary

Randomized trial on the efficacy of two non steroidal drugs in the prevention of skin damage induced by radiotherapy

The aim of this study is to evaluate the reparative properties of the Restitutio Restructuring Cream (RRC) produced in two formulations for the skin injuries caused by radiation in patients undergoing radiotherapy treatment: "A formulation", cutaneous emulsion based on alginates; "B formulation", cutaneous emulsion based on alginates, hyaluronic acid, and beta-glucan. A total of 64 patients were recruited in the protocol: 52 patients with breast cancer operated on conservatively and requiring postoperative radiotherapy and 12 patients with head and neck cancer requiring curative radiotherapy. Patients were randomized to receive, during radiotherapy, a topical treatment with RRC on the irradiated skin. Overall 39 patients reported skin toxicity at grade 1. Grade 2 of skin toxicity was observed in only 6 patients with breast cancer. We have not observed any cases of grade 3 or more of skin toxicity requiring break in radiotherapy treatment. Results were assessed not only in terms of grade and overall reduction in toxicity but also in terms of full regression of skin lesions with "ad integrum restitutio" and in terms of rapidity of repair of radio-induced damage. Both formulations of cream used showed good effectiveness though better for "B formulation"; "ad integrum restitutio" was good and occurred on average within 5 and a half weeks.

KEY WORDS: *Radio-dermatitis, Radio-induced skin injuries, Topical treatment*

Introduction

Acute radio-dermatitis is a common collateral effect during radiotherapy for the treatment of several tumors such as those of head and neck, breast, soft tissue sarcomas as well as cutaneous cancers[1]. Radio-dermatitis can appear with different grades, until it becomes, in the worst case, a real burn[2]. Symptoms of radio-dermatitis can be quite significant (itch, burning, prickling pain) and sometimes they can necessitate a break in treatment. The radiation oncologists classifie acute damage from radiations according to a scale proposed by RTOG-EORTC[3,4], reported in Table 1.

The intensity of reactions depends on several factors related to the fractionation and total radiotherapy doses: the cutaneous injuries usually appear in doses over 40-45 Gy and in using hypofractionated treatment (high doses for a session)[5]. Reaction intensity also depends on the kind of energy used: electrons release more energy in the skin and they may cause more damage than photons, with increased incidence of fibrosis and teleangectasia. Furthermore, when using photons, those with low-energy have a more superficial build-up than those of high energy determining more toxicity on the skin and subcutaneous soft tissues. Cutaneous injuries were also more common using cobalt or orthovoltage therapy.

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Table 1.

RTOG-EORTC acute skin toxicity scale.

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change over baseline	Follicular, faint or dull erythema; epilation, dry desquamation or decreased in sweating.	Tender, bright erythema; patchy, moist desquamation or moderate edema.	Confluent, moist desquamation other than skin folds; pitting edema.	Ulceration, hemorrhage, necrosis.

Radiation-induced skin injuries are more common in the radiotherapy of breast cancer (Figure 1) (where used doses are of 50 Gy over the whole breast followed by a boost on the surgical bed of 10-16 Gy) or in the head and neck cancers (where in the case of radical intent used doses are higher, up to 70 Gy) and when photons with low energy (about 6 MV) sometimes associated with electrons are used. Furthermore, in the treatment of these diseases quite simple arrangements of beams are used to reduce and minimize the occurrence of side effects. Other factors that may affect the intensity of skin reactions are: the specific area of skin treated (being more frequent in locations such as the infra-mammary furrow, the neck, the axillae, the inguinal folds), the phototype (more common in light skin), the intrinsic skin sensitivity, the size of the mammary gland and the possible concurrent or sequential use of chemotherapy, today increasingly frequent[6].

Currently there is no standard approach for the prevention and treatment of radio-induced skin lesions, although several studies have been published on the use of various kinds of topical drugs (aqueous creams, aloe vera-based creams, almond oil-based, with chamomile, hyaluronic acid, sucralfate, gentian violet or topical corticosteroids, etc...). The most part of this studies doesn't show however a clear superiority of an agent on the other[7,10]. The review published in 2006 by Bolderston and coll, concludes that there is insufficient evidence to support or refuse specific topical agents for prevention or management of acute skin reaction[9].

Also *McQuestion* in his paper published in 2006, draws same conclusions[10].

Table 2 summarises some of the most recent studies of literature (from 2000 to today) on this topic[11,17].

Our study aims to assess the reparative properties of the *Restitutio Restructuring Cream* (RRC) produced by the *Ganassini Institute* in two formulations (A and B) on skin injuries caused by radiation in patients undergoing radiotherapy treatment.

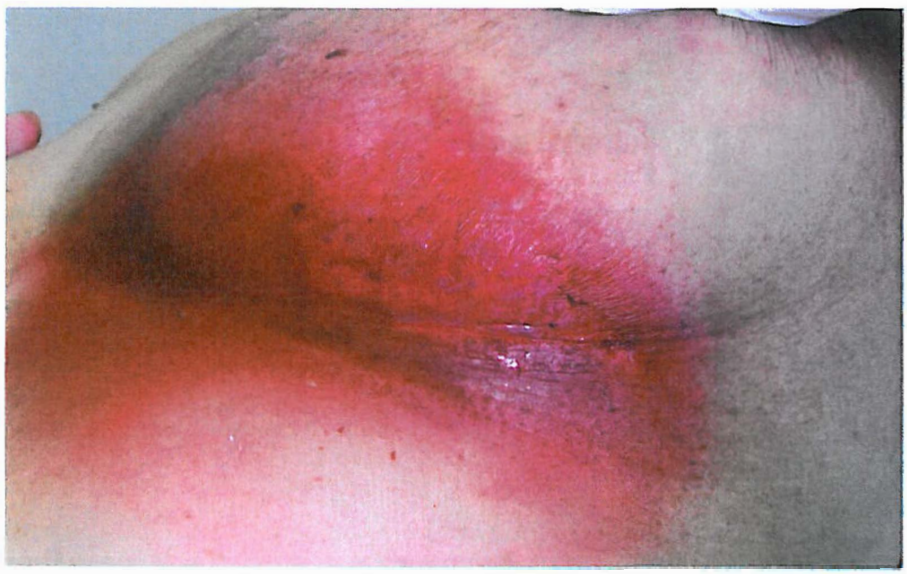

Figura 1.

Example of grade 2 acute skin toxicity in radiation treatment for breast cancer.

Table 2.

Recent clinical studies of literature.

Clinical study	Year	Kind of study	N. pts	Site	Results
Röper B et al. (Strahl Onk) (11)	2004	Phase III (Thêta-cream vs Bepanthol lotion)	20	Breast	No differences in side effects; higher cost and problems with skin marks.
Pommier P et al. (JCO) (12)	2004	Phase III (Calendula vs Trolamine)	254	Breast	Calendula better ($p < 0.001$)
Szumacher E et al. (IJROBP) (13)	2001	Phase II (Biafin)	60	Breast	G2 83%; G3 2% No break or delay of RT
Fisher J et al. (IJROBP) (14)	2000	Phase III (Biafin vs BSC)	172	Breast	No differences $p = 0.77$
Leonardi MC et al. (Eur J Dermatol) (15)	2008	Double-blind random (MAS065D vs vehicle)	40	Breast	MAS065D Better ($p < 0.0001$)
Wells M et al. (Radiother Oncol) (16)	2004	Phase III (Sucralfate vs aqueous cream vs no cream)	357	Breast, H&N Anorectal area	No differences

Materials and methods

This is a prospective study conducted in a project for the continuous improvement of quality assurance in radiotherapy[18]. It was conducted at *Istitute for Cancer Research and Treatment* (IRCC) *of Candiolo (Turin)* in 2007.
The study aimed to evaluate the reparative properties of the RRC produced in two formulations (A and B) on injuries caused by radiation in patients undergoing radiotherapy treatment.
Inclusion criteria were:

- informed consent
- patients with breast cancer operated on conservatively and requiring postoperative radiotherapy treatment
- patients with head and neck cancer requiring radiotherapy with radical intent
- Karnofsky performance status 90-100
- patients with negative history for allergy.

Exclusion criteria were:

- patients with history of cutaneous hypersensitivity to topical substances
- patients with positive history for allergy
- patients with connective tissue diseases
- patients with history of psychological problems that could reduce compliance to treatment protocol.

A total of sixty-four patients, candidate for radiation therapy, were recruited in the protocol: 52 patients with breast cancer operated on conservatively and requiring postoperative radiotherapy treatment and 12 patients with head and neck cancer requiring radiotherapy with radical intent.
Administered doses for patients irradiated for breast cancer were as follows: 50 Gy in 25 fractions to the whole breast with 6 MV photons, over 5 weeks, and then a boost to the surgical bed of 10 Gy in 5 fractions with 6-9 or 12 MeV electrons, for a total dose of 60 Gy.
Patients treated with radical intent for head and neck cancer received a prophylactic dose of 50-54 Gy to the lymph nodes at risk, 60-66 Gy to the gross lymph nodes volume and 66-70 Gy to the gross tumor volume. The fractionated dose was of 180-00 cGy per day. 6 MV Photons were used, sometimes associated with 6-9 or 12 MeV electrons.
Patients were randomized to receive, during radiotherapy, a topical treatment on the irradiated skin by means of the RRC produced in two formulations indicated as A or as B.
Of the 52 breast cancer patients, 26 were treated with the "A formulation" and 26 with the "B

formulation". Of the 12 head and neck cancer patients, 6 were treated with the "A formulation" and 6 with the "B formulation".
The cream was given to the patients by the Radiotherapy nurse before the start of treatment. The nurse was responsible for explaining to the patients the mode and timing of administration. Patients self administrated the cream, in quantities of about 3 grams per application from the first day of radiotherapy until the tenth day after the end of radiation treatment. Cream was administered twice a day, three hour before and immediately after the session of radiotherapy.
Randomization was generated by computer and neither the patients nor the physicians and nurse knew which was formulation used by the patient for the whole duration of the radiation course. All patients underwent a baseline physical examination before the start of radiotherapy and then every week, during the treatment, or more if needed. Finally, at the end of the radiation course, every week during the first month of follow-up. Acute skin toxicity was evaluated according to the RTOG-EORTC scale (Table 1). Compliance to the protocol was of 100%.

Table 3.

Radio-induced acute skin toxicity in patients treated for breast cancer.

Grade	A Formulation (n° patients)	B Formulation (n° patients)
G0	9	6
G1	15	16
G2	2	4
G3	0	0
G4	0	0
Total patients	26	26

Table 4.

Radio-induced acute skin toxicity in patients treated for head and neck cancer..

Grade	A Formulation (n° patients)	B Formulation (n° patients)
G0	2	2
G1	4	4
G2	0	0
G3	0	0
G4	0	0
Total patients	6	6

Results

Toxicity observed in the 52 patients with breast cancer is shown in Table 3 (Figure 2A). Toxicity observed in the 12 patients treated for head and neck cancer is shown in Table 4 (Figure 2B).
Overall 39 patients reported a grade 1 of skin toxicity: 31 treated for breast cancer and 8

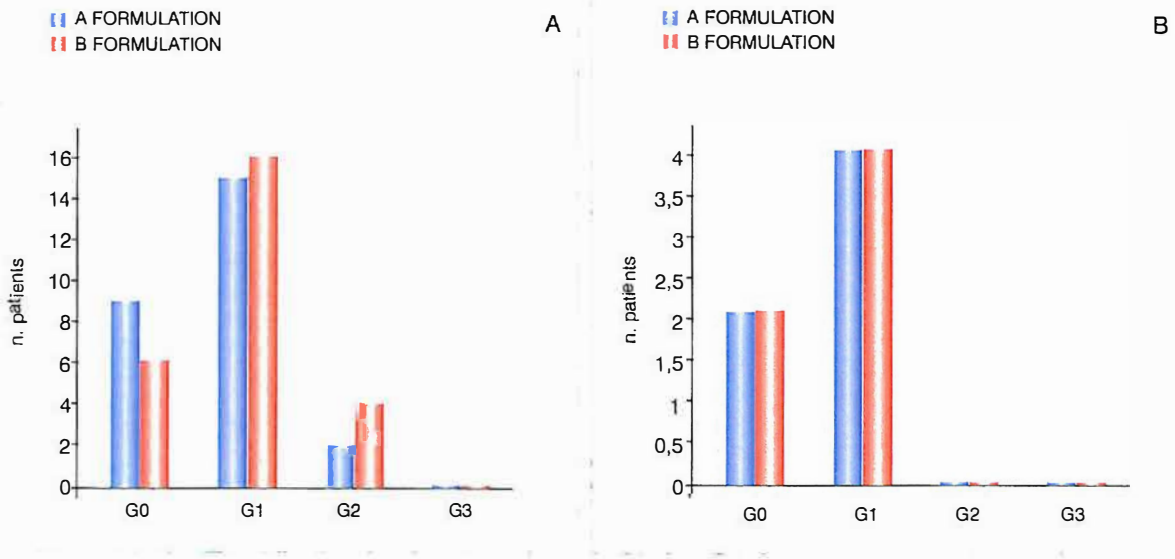

Figura 2.

Acute skin toxicity distribution in patients treated for breast cancer (A) and in patients treated for head and neck cancer (B).

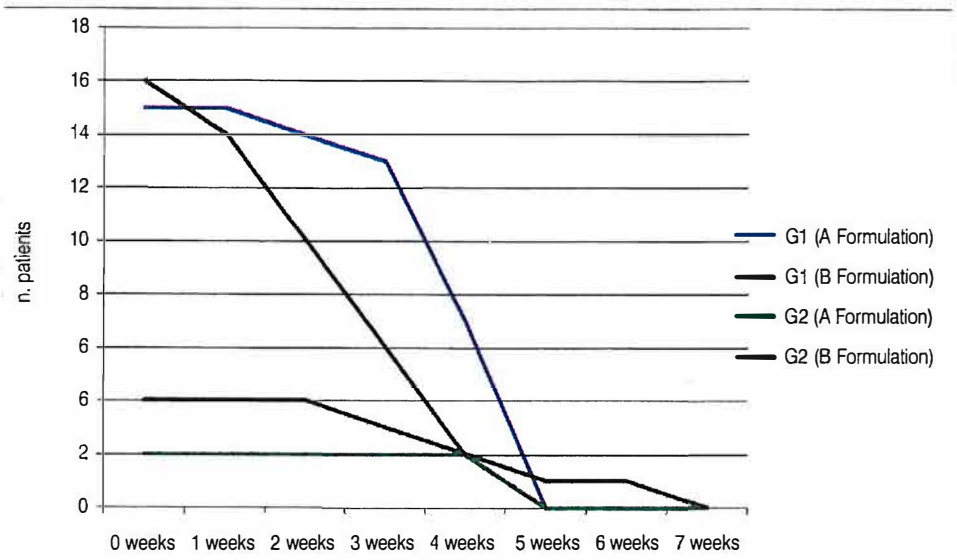

Figura 3.

Regression time of radio-induced acute skin injuries in patients treated for breast cancer. G1: grade 1 of acute skin toxicity, G2: grade 2 of acute skin toxicity (RTOG-EORTC scale).

treated for head and neck cancer. Grade 2 of skin toxicity was observed in only 6 patients with breast cancer.

Of 31 patients with breast cancer showing grade 1 of acute skin toxicity, 15 were treated with "A formulation" and 16 with "B formulation". Of 15 patients treated with "A formulation", two recovered within 3 weeks and 13 within 5 weeks. Of 16 patients treated with "B formulation", 10 showed regression of skin lesions within 3 weeks and 6 within 5 weeks (Figure 3). Of 6 patients with breast cancer showing grade 2 of acute skin toxicity, two were submitted to "A formulation" treatment and 4 to "B formulation". The first two patients (treated with "A formulation") recovered within 5 weeks, while of the remaining 4 (treated with "B formulation") 3 showed regression within 5 weeks and one within 7 weeks (Figure 3).

Of 8 patients treated for head and neck cancer showing grade 1 of acute skin toxicity, 4 were submitted to topical "A formulation" and 4 to

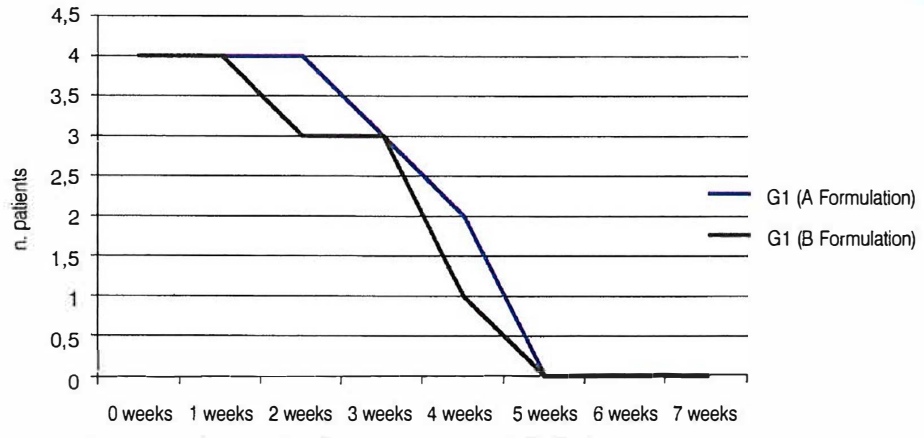

Figura 4.

Regression time of radio-induced acute skin injuries in patients treated for head and neck cancer. G1: grade 1 of acute skin toxicity, G2: grade 2 of acute skin toxicity (RTOG-EORTC scale).

"B formulation". In these patients regression of skin lesions was observed as follows: in those treated with "A formulation" 1 was cured within 3 weeks and the remaining 3 within 5 weeks; in patients treated with "B formulation" 1 showed recovery within 3 weeks and the remaining 3 within 5 weeks (Figure 4).

Conclusions

One of the main clinical activities of the physician radiotherapist is the monitoring of patients throughout the treatment course. During this activity the physician, sometimes supported by the radiotherapy nurse, has to treat any radio-induced skin lesions.

The approach to this problem may be different depending on the philosophy of the centre. In some radiotherapy centres, topical drugs are generally not prescribed, unless of they are hygienic-behavioral type, until skin lesions appear. In this case the physician prescribes topical products if necessary. In other centres, targeted and planned protocols of intervention for disease are active. In the specific case of breast cancer topical application of a specific cream is suggested from the third week of radiation treatment. In other cases the prophylactic prescription of topical products is established from the beginning until the end of radiotherapy or sometimes even for one or two weeks after the end of treatment.

Actually, data in recent years are lacking since with the use of high-energy radiation produced by linear accelerator (LINAC), acute skin toxicity is reduced significantly compared to the period in which cobalt therapy was routinely used.

Therefore, data indicating a definitive "gold standard" treatment are not reported in the literature[9-17]. *Bolderston et al.*, in their review concludes that skin washing, including gentle washing with water alone with or without mild soap, should be permitted in patients receiving radiation therapy to prevent acute skin reaction and no sufficient evidence there is to support or refuse a specific topical agent to prevent or menage acute skin reactions[9]. The same conclusions are derived by *McQuestion* in his study[11h10].

Therefore, we believe that each Institution should establish, on the basis of internal protocols, common behavioral and data collection guidelines, taking in account also the cost-benefit balance in term of expences for the patients.

Our study would make a contribution to this topic; in agreement with the producer (*Ganassini Institute*) we tested the reparative properties of two creams with different characteristics in order to evaluate which of them would offer the best result in daily clinical practice. Results were assessed not only in terms of toxicity grade and overall reduction in toxicity but also in terms of full regression of skin lesions until "ad integrum restitutio" and in terms of rapidity of radio-induced damage repairs.

This is of considerable importance if one considers that sometimes a severe grade of skin toxicity may require a treatment break that should be avoided since it is an unfavorable prognostic factor for expected outcome. In our study no grade G3-G4 toxicity was observed. This fact allowed that radiation treatment was finished without interruptions.

In our study we can draw the following conclusions: we have not observed, as in many other published studies, any cases of grade 3 or more skin toxicity requiring treatment break; both formulations of used cream, showed good effectiveness, although with the "B formulation" the damage repair was overall quicker than with the "A formulation": "ad integrum restitutio" was good and was on average within 5 weeks and half.

The more grade 2 toxicity observed with "B formulation" could be explained with the fact that in this group of patients there were 3 patients with bulky breasts versus only 1 in the other group.

Compliance to protocol was of 100% both because the two formulations did not cause uncomfortable side effects to the patients and because there was a close collaboration with the nurse who constantly and carefully followed our patients.

In conclusion we believe that tested creams can be considered an effective coadjuvant in patients treated with radiotherapy for breast cancer and for head and neck cancer.

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