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RESEARCH ARTICLES

Prophylaxis with a cream containing urea reduces the incidence and severity of radio-induced dermatitis

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Abstract
Introduction Radio-induced dermatitis is one of the most frequent side effects of radiotherapy. Among the commercially available products for the care of irradiated skin is a hydrating lotion containing 3% urea, polidocanol and hyaluronic acid. Its effectiveness for preventing the appearance of radiodermatitis or reducing its severity has been studied on a number of occasions.
Objective To evaluate the effectiveness of "intensive use" of the lotion containing 3% urea, polidocanol and hyaluronic acid for preventing the appearance of acute radiodermatitis and controlling its severity.
Material and methods Prospective observational study in 98 patients with breast cancer with a 10-week follow-up period. Skin toxicity (RTOG/EORTC scale) was evaluated weekly. To study the effectiveness we compared incidence and grade of toxicity with a sample of 174 breast cancer patients (control sample) treated in our centre during 2006 who used skin-support measures at the start of the radiotherapy or the occurrence of radiodermatitis.
Results The proportion of patients who did not develop radiodermatitis was significantly higher in the intensive use group (27.6% vs. 15.5%; $p<0.05$; OR: 2.07). Compared with the same lotion in standard conditions, the intensive use group showed lower incidence of radiodermatitis ($p<0.01$), lower grade of toxicity ($p<0.001$) and lower proportion of radiodermatitis grade 2 or higher ($p<0.01$).
Conclusions Intensive use of the lotion doubles the likelihood that breast cancer patients will not develop radiodermatitis during radiotherapy. Furthermore, compared with standard use, intensive use is more effective in reducing the incidence of skin toxicity and skin toxicity grade 2 or higher.

Keywords Radio-induced dermatitis · Prophylaxis with a cream containing urea · Breast cancer patients

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Introduction

Radiotherapy (RT) is an essential part of treatment for many tumours. However, it not only acts on tumour cells, but may also affect healthy tissues near the irradiated area.

The skin is one of the tissues most affected by ionising radiation. It is estimated that between 80 and 90% of irradiated patients experience some degree of dermatitis, ranging from the mildest forms of erythema to the most severe cases with moist desquamation and ulceration [1].

Even though radio-induced dermatitis is one of the most frequent side effects of radiotherapy, there are currently no

standardised guidelines for its prevention and treatment. At present, topical products with active agents are commonly used to palliate the effects on the skin, alleviate patient discomfort and avoid treatment interruption [2].

Although researchers have assessed the effectiveness of various topical and oral agents for the prevention and treatment of radiodermatitis for several years, no consensus has been reached on an ideal strategy. The topical products studied include creams or lotions containing corticoids, sucralfate, trolamine, calendula, aloe vera, camomile or hyaluronic acid [3]. The results for these agents are conflicting; not all of them are reported to reduce skin toxicity, although they are still used in clinical practice.

Among the commercially available products for the care of irradiated skin in Spain is a hydrating lotion containing 3% urea, polidocanol and hyaluronic acid (Ureadin® Rx Rd, ISDIN, Spain). The effectiveness of this lotion for preventing the appearance of radiodermatitis or reducing its severity in patients undergoing radiotherapy has been studied on a number of occasions. In a placebo-controlled study in 48 patients using non-invasive instruments for biophysical measurement (corneometer, TEWAmeter, D-Squam and colorimeter) the lotion prevented dehydration by the third week of radiotherapy and halted desquamation and the transepidermal water loss (TEWL) increase by the end of the treatment [4]. Another placebo-controlled study in 54 patients treated for breast cancer showed that the lotion delayed the appearance of radiodermatitis and reduced the intensity of the accompanying symptoms (pruritus and pain) [5]. Another double-blind, randomised, controlled trial in 95 patients receiving radiotherapy for different types of tumour found that use of the lotion lowered the risk of developing radiodermatitis between three and eight times and reduced the intensity of symptoms [6]. This study also found a relation between the quantity of lotion used and the severity of the condition [7].

In view of these results and the relation found between the quantity of lotion and the severity of radiodermatitis, the present study aimed to evaluate the effectiveness of intensive use of the lotion containing 3% urea, polidocanol and hyaluronic acid for preventing the appearance of acute radiodermatitis and controlling its severity. In previous studies and in standard practice the lotion is usually applied twice a day, beginning either at the same time as radiotherapy or at most ten days before. In the "intensive use" protocol applied in this study the lotion is applied three times a day, beginning two or three weeks before RT.

Material and methods

Patients and treatment

This prospective, observational study was performed between August 2007 and October 2008 in a cohort of 98 patients diagnosed with breast cancer and receiving radiotherapy at the Radiation Oncology Department of the Hospital General de Catalunya with a 10-week follow-up period. Prior to the start of the study, the protocol and all the materials were approved by the hospital's ethical committee.

Patients over 18 years diagnosed with breast cancer, previously treated with conservative surgery and scheduled to begin external radiotherapy were consecutively included in the study after giving signed informed consent. During the simulation phase, subjects were provided with the hydrating lotion containing 3% urea and instructed to apply it three times daily on the area to be irradiated, beginning two or three weeks before the start of radiotherapy and continuing throughout the treatment.

Adjuvant radiotherapy after conservative surgery was scheduled, comprising of irradiation of the entire mammary gland with photons up to a maximum dose of 50 Gy in 25 fractions of 2 Gy/day, followed by an electron boost to the surgical bed and safety margins with the same fractioning procedure, until a total dose of between 60 and 70 Gy was reached. One patient also required irradiation of the internal mammary lymph nodes.

Weekly controls were conducted in all patients throughout the period of external radiotherapy. Skin toxicity was evaluated weekly using the RTOG/EORTC acute toxicity scale. Patients rated pain, itching, reddening, desquamation and impact on skin welfare (quality of life) using visual analogue scales (VAS, 0 to 10). At the end of the study physicians and patients were asked to rate the effectiveness, tolerability and cosmetic properties of the lotion on scales of 0 to 3 (0=poor, 1=moderate, 2=good, 3=excellent). The patients were also asked to give an overall score out of ten.

The control group comprised a sample of 174 patients with breast cancer undergoing conservative surgery and treated with radiotherapy at our centre in 2006, which had used some kind of skin treatment at the start of radiotherapy or on presentation of radiodermatitis. The sample was obtained from a review study of 235 clinical histories of patients with breast cancer undergoing radiotherapy, designed to determine the incidence of skin toxicity at our centre [8].

Statistical analysis

The statistical analysis was performed using the statistical software package SPSS 13.0 for Windows.

Descriptive statistics (frequencies and proportions) were used to assess the overall incidence of radiodermatitis, the week in which toxicity appeared, initial grade of radiodermatitis (grade of toxicity at the time of the physician's diagnosis of radiodermatitis) and deterioration of radiodermatitis (as the grade of toxicity may increase during the weeks following diagnosis). The patients' subjective evaluations of the skin symptoms were studied on the basis of the mean score obtained for each symptom during the follow-up examinations.

Table 1 Characteristics of the sample

Age (years)	
Mean [CI 95%]	59.1 [57.2–61.0]
Surgical treatment (*n*=96)	n (%)
Conservative	96 (100%)
Chemotherapy (*n*=95)	
No	65 (68.4%)
Yes	30 (31.6%)
Hormone therapy (*n*=93)	
No	21 (22.6%)
Yes	72 (77.4%)
Radiotherapy	
Total mean dose (Gy)	62.17
[CI 95%]	61.0–63.3
Treatment volume (*n*=97)	n (%)
Breast alone	96 (99.0%)
Breast and lymph nodes	1 (1.0%)
Fractioning (*n*=97)	
5 fractions of 2 Gy/day/week	97 (100.0%)
Type of radiation (*n*=96)	
Photons	15 (15.6%)
Photons and electrons	81 (84.4%)
Photon energy (*n*=77)	2 (2.1%)
1.23 MV	2 (2.6%)
6 MV	75 (97.4%)
Electron energy (*n*=77)	
6 MeV	26 (33.8%)
9 eV M	51 66.2%) (

To study the effectiveness of intensive use of the lotion as prophylaxis for radiodermatitis we compared the percentages of patients with radiodermatitis, the grade of toxicity and the percentage of cases with radiodermatitis grade 2 or higher in the intensive use group and the control sample. Then, to determine whether intensive use of the lotion is more effective than standard use, we compared the results with those of the subsample of 20 control patients who had used the same lotion from the start of radiotherapy or from the moment they presented radiodermatitis. Mann–Whitney *U* tests were used to compare grades of toxicity and Chi-square tests to compare the percentages, calculating the Odds Ratio.

The effects of chemotherapy and hormone therapy on the appearance of radiodermatitis were determined by comparing treated and untreated patients, using Pearson's Chi-square tests and the Odds Ratio.

Results

Characteristics of the sample and treatment

All patients were women with a mean age of 59 years [R: 57.2-61.01]. In addition to surgical treatment and radiotherapy, 31.6% also received chemotherapy and 77.4% hormone therapy. The duration of radiotherapy ranged between 6 and 9 weeks, with a mean of 48 days. The planned treatment volume (PTV) included the breast without lymph node chains in 99% of cases and the breast with lymph node chains in only one case. The mean radiotherapy dose was 62.17 Gy [95% CI: 61.0–63.3 Gy], in fractions of 2 Gy per day, 5 days per week. In 97.4% of cases, 6-MeV photons were used. Boost energy ranged between 6 and 12 MeV, being 9 MeV in 66.2% of cases (Table 1).

Radiodermatitis

The overall rate of radiodermatitis was 72.4%. In all, 51.0% of patients presented toxicity grade 1, 20.4% grade 2 and 1.0% grade 3. Although the first case of skin toxicity appeared in the third week of treatment, in more than 87% of patients radiodermatitis appeared between weeks 5 and 7 (Table 2).

The initial grade of radiodermatitis recorded was grade 1 in 62.2% of cases, grade 2 in 9.2% and grade 3 in one case. In 15.5% the radiodermatitis worsened during the weeks of follow-up.

The severity of the clinical symptoms (pain, itching, reddening, desquamation and impact on wellbeing) reported by the patients was negligible, with a range of maximum scores between 0 and 0.9 on the 0–10 VAS throughout follow-up.

Radiotherapy was interrupted in only two patients: one due to radiodermatitis grade 3 (14-day interruption) and another who required a vertebroplasty (40-day interruption).

Table 2 ROTG/EORTC toxicity grade by week of treatment

Grade RTOG/EORTC	0	1	2	3	*n*
Week 1	96 (100.0%)	–	–	–	96
Week 2	96 (100.0%)	–	–	–	96
Week 3	95 (99.0%)	1 (1.0%)	–	–	96
Week 4	93 (96.9%)	3 (3.1%)	–	–	96
Week 5	78 (79.6%)	15 (15.3%)	4 (4.1%)	1 (1.0%)	98
Week 6	51 (52.6%)	36 (37.1%)	10 (10.3%)	–	97
Week 7	48 (52.2%)	34 (37.0%)	10 (10.9%)	–	92
Week 8	39 (61.9%)	24 (38.1%)	–	–	63
Week 9	35 (94.6%)	2 (5.4%)	–	–	37
Week 10	21 (100.0%)	–	–	–	21

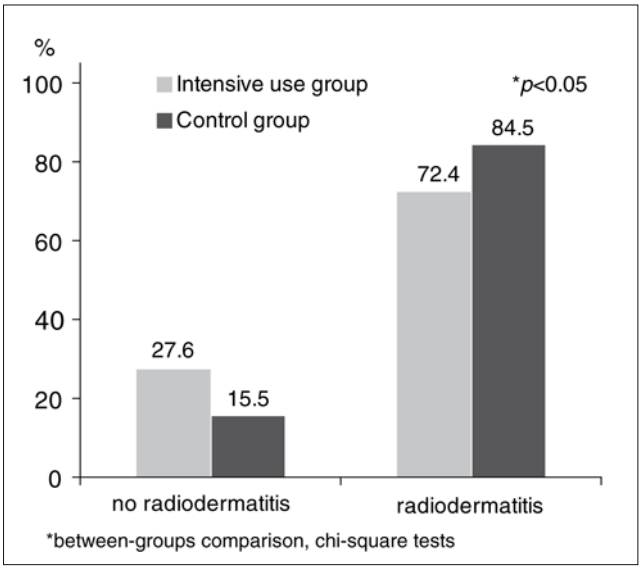

Fig. 1 Rates of patients presenting and not presenting radiodermatitis in the intensive use group and the control group

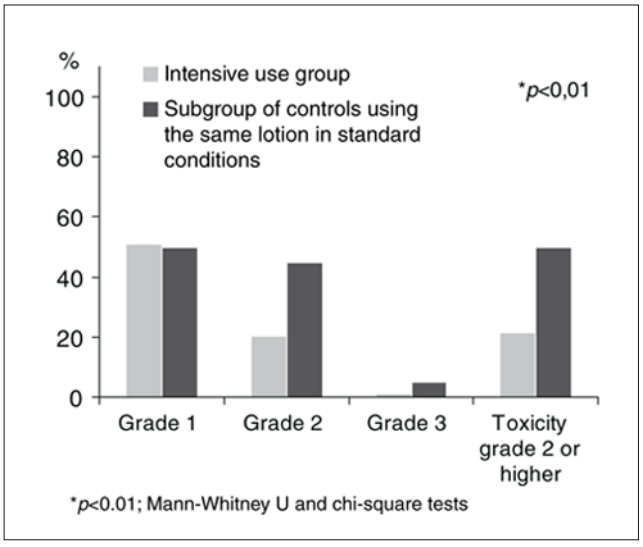

Fig. 3 Grade of skin toxicity (RTOG/EORTC) in the intensive use group and the subgroup of controls using the same lotion in standard conditions

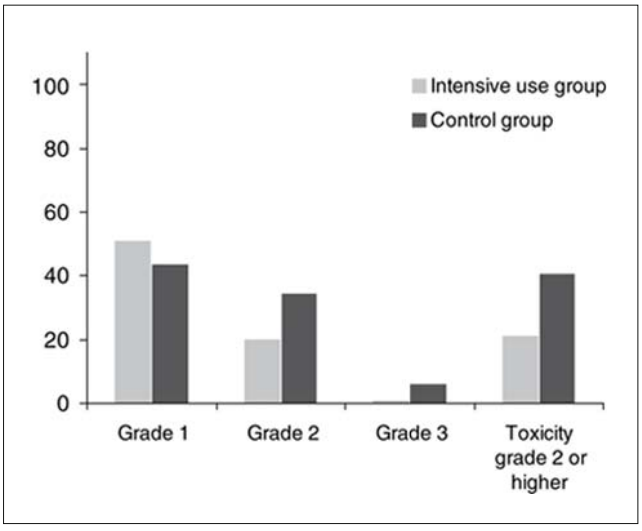

Fig. 2 Skin toxicity grade according to the ROTG/EORTC in the intensive use group and the control group

The incidence of radiodermatitis was similar in patients who underwent chemotherapy and in those who did not (73.8% vs. 73.3%; n.s.). This incidence did not differ significantly in the case of hormone therapy (75.0% in treated patients vs. 66.7% in untreated patients; n.s.).

Comparison with the control group

The two samples were homogeneous in terms of treatment. No significant differences were found with regard to total dose (mean: 62.18 Gy [95% CI: 61.3–63.0] vs. 62.17 Gy [95% CI: 61.0–63.3]) or dose fractionation (2Gy/5 days/ week, 96.1% vs 100%), or treatment with chemotherapy (34.4 vs. 31.6% n.s.)

The proportion of patients who did not develop radiodermatitis was significantly higher in the intensive use group than in the controls who initiated skin treatment at the beginning of radiotherapy (27.6% vs. 15.5%; $p<0.05$; OR: 2.07 [95% CI: 1.13–3.79]) (Fig. 1).

The incidence of radiodermatitis was significantly lower in the intensive use sample (72.4% vs. 84.5%; $p<0.05$; OR: 0.48 [95% CI: 0.26–0.88]). The grade of toxicity was also significantly lower in the intensive use sample ($p<0.001$), as was the proportion of patients that developed toxicity grade 2 or higher (21.4% vs. 40.8%; $p<0.001$; OR: 0.39 [95% CI: 0.22–0.70]) (Fig. 2).

Compared with the subgroup of controls who had used the lotion in standard conditions, the intensive use group showed lower incidence of radiodermatitis (72.4% vs. 100%; $p<0.01$; OR: 4.7 [95% CI: 1.5–14.7]), lower grade of toxicity ($p<0.001$) and lower proportion of radiodermatitis grade 2 or higher (21.4% vs. 50%; $p<0.01$; OR: 0.27 [95% CI: 0.10–0.74]) (Fig. 3).

Final ratings of the lotion by physicians and patients

Both physicians and patients rated the effectiveness, tolerability and cosmetic properties of the lotion as good or excellent. Only two patients presented adverse reactions during the study: one follicular keratosis and one allergic reaction. Both were mild and were attributed by the dermatologist to the application of the lotion. The episodes resolved within a week of discontinuation of the lotion and initiation of low-dose corticoid and antihistaminic treatment.

Discussion

Our results indicate that prophylactic use of this lotion containing urea, polidocanol and hyaluronic acid, starting two or three weeks prior to initiation of radiotherapy and continuing until its termination, reduces the overall incidence of radiodermatitis and also the incidence of radiodermatitis of grade 2 or higher.

The toxic effects of ionising radiation on the skin begin to appear at doses of 20–25 Gy, between the second and fourth weeks of treatment. An inflammatory reaction develops, mediated by the release of cytokines which causes erythema; the destruction of the sweat glands leads to dryness and the loss of the hair follicles causes depilation. The stimulation of the melanocytes leads to hyperpigmentation in the areas treated. Progressively the cells of the stratum basalis decrease in number leading to dry desquamation, accompanied by pruritus. If the damage continues, from the fourth or fifth week moist desquamation develops, characterised by the appearance of serous exudation and exposure of the dermis [3].

The discomfort caused by radio-induced dermatitis may lead patients to interrupt treatment and thus compromise the final result. Initially treatment is based on washing the skin of the irradiated area with soap and water and using hydrating lotions and creams to reduce the irritation and stinging sensation that accompany the dry desquamation [2].

Most studies of the effectiveness of different compounds for preventing and treating radiodermatitis are too small to justify their standardised use in clinical guides, in spite of their positive results. In a randomised double-blind trial with 49 patients diagnosed with breast cancer, the use of a cream with corticoids significantly reduced the grade of dermatitis compared with an emollient cream [9]. Previously, another placebo-controlled study in 50 patients with breast cancer showed that the use of a cream with sucralfate significantly reduced the incidence of radiodermatitis grade 2 [10]. In a controlled trial with a larger patient sample, Pommier et al. compared the effects of a cream with calendula and a cream with trolamine in 254 patients, finding that the product containing calendula was more effective in preventing toxicity of grade 2 or higher [11].

The hydrating lotion used in this study (Ureadin Rx Rd) is formulated specifically for the care of irradiated skin. Among other active agents, it contains urea, polidocanol and hyaluronic acid. Urea is a natural substance that is a component of the natural hydration factor of the skin. Its function is to retain water in the stratum corneum so as to preserve the skin's biomechanical properties and to maintain the balance of humidity and flexibility. Applied topically, urea is absorbed by the epidermis, alleviating symptoms and increasing the sensation of comfort, softness and hydration. Widely applied in dermatological and cosmetic products, its use in the form of a lotion in patients undergoing radiotherapy helps to protect and maintain the integrity of the skin, preventing dehydration and reducing the TEWL increase and desquamation following treatment [4].

Hyaluronic acid is a natural biopolymer with a high capacity for water retention. It is the main component of the extracellular tissue in the dermis and provides mechanical and structural support. It also plays a key role in the process of wound repair. Its effect on radio-induced skin toxicity was investigated by Liguori et al. in 134 patients treated for cancer of the head and neck, pelvis or breast; in that study, the prophylactic use of a cream containing hyaluronic acid significantly reduced the degree of radiodermatitis [12].

Polidocanol is an ethoxylated fatty alcohol with multiple applications in medicine. In dermatology it is used to relieve pruritus thanks to its local anaesthetic properties when applied topically. Preparations of polidocanol combined with urea have proved to be efficient in the treatment of skin pathologies characterised by dryness, desquamation and pruritus.

Studies of Ureadin® indicate that when used in standard conditions (two applications a day, initiating treatment at the same time as radiotherapy or at most ten days previously), it is able to reduce the risk of radiodermatitis, delaying its appearance and reducing its intensity [5, 6].

In the present study, in which the lotion was used intensively (three times a day, initiating treatment two to three weeks prior to radiotherapy), the overall incidence of skin toxicity in patients was 72%, below the rates reported in the literature and by Cabeza et al. in their study of patients with breast cancer treated with conservative surgery (95%) [6]. Furthermore, the rate of radiodermatitis was significantly lower than in the control sample of patients from our own centre, a finding that demonstrates the effectiveness of intensive application of the lotion, even bearing in mind the possible differences in practices at particular hospitals.

Our study therefore suggests that intensive prophylactic use of this lotion prevents the development of skin toxicity in more than a quarter of patients. Furthermore, in comparison with our data from 2006, our current results indicate that patients irradiated for breast cancer who use this hydrating lotion intensively are two times less likely to develop radiodermatitis than those using the same lotion in standard conditions.

The severity of the radiodermatitis with the lotion used intensively was also significantly lower, often reducing the risk of developing toxicity grade 2 or higher by more than half.

In most cases, toxicity appeared between week 5 and week 7. Bearing in mind that fractionated doses of 5×2 Gy were administered, this indicates that toxicity appears at a total accumulated dose of 50 Gy. Normally, radiodermatitis appears between the second and the fourth weeks when accumulated doses of 20 or 25 Gy are reached, that is, considerably earlier [3]. This delay in the appearance of the condition corroborates the results of Muñoz García et al. [5], who found that, in comparison with a placebo, this lotion managed to delay the appearance of radiodermatitis by a week.

Conclusion

Our data indicate that intensive use of the lotion doubles the likelihood that breast cancer patients will not develop radiodermatitis during radiotherapy and reduces by more than half the risk of developing toxicity grade 2 or higher. Furthermore, compared with standard use, intensive use is more effective in reducing the incidence of skin toxicity in general, and of skin toxicity grade 2 or higher in particular, and is associated with high tolerability and acceptance by both physicians and patients.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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