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Prevention of cutaneous damages induced by radiotherapy in breast cancer: an institutional experience

Vincenzo Ravo[1], Maria Grazia Calvanese[2], Rossella Di Franco[2], Vincenzina Crisci[2], Paola Murino[1], Roberto Manzo[1], Anna Morra[3], Fabrizio Cammarota[1], and Paolo Muto[4]

[1]UOC Radioterapia PO Ascalesi ASLNA1 Naples; [2]Dipartimento Radiologia e Radioterapia Seconda Università di Napoli; [3]UOC Radioterapia Istituto Europeo di Oncologia, Milan; [4]UOC Radioterapia INT Pascale Naples, Italy

ABSTRACT

Background and aims. A minimal part of patients treated with radiotherapy on the entire breast may present an acute, subacute or chronic cutaneous damage of the healthy tissues involved in the radiation fields. The aim of this retrospective study was to evaluate the most efficient topical hydrating treatment in the prevention of cutaneous radio-induced acute effects in breast cancer.

Material and methods. From February 2009 to March 2010, 100 patients affected by breast cancer have been recruited, all of the female sex and with an average age of 47 years. The following topical treatments were compared: Pure vitamin E (Vea lipogel®), Omega-3,6,9 (Quinovit®), Betaglucan, sodium hyaluronate (Neoviderm®), *Vitis vinifera* A.s-I-M.t-O.dij, (Ixoderm®), natural triglycerides-fitosterols (Xderit®). All enrolled patients were subjected to breast conservative treatment (quadrantectomy with or without homolateral axillary dissection) and without prosthesis positioning, in combination or not with hormonal treatment. Evaluation of the cutaneous acute toxicity was defined according to the RTOG scale either during radiotherapy and during follow-up (3 months after radiation treatment).

Results. All patients completed the radiotherapy; 62% of patients presented G0-G1 cutaneous toxicity, 28% have developed G2 cutaneous toxicity, 10% have developed G3 toxicity; no patient presented G4 toxicity. Analysis of the data revealed a correlation between the topical treatment used and the incidence of cutaneous toxicity.

Conclusions. Of the patients who used the cutaneous hydrating creams – betaglucan, sodium hyaluronate (Neoviderm®) and *Vitis vinifera* A.s-I-M.t-O.dij (Ixoderm®) – during the radiation treatment, 80% developed G0-G1 toxicity and 20% G2 toxicity. The patients who used the other hydrating creams tested in the study manifested not only G1-G2 toxicity but also some G3 toxicity. Chemotherapeutic treatment with taxanes and/or anthracyclines did not result in an increased breast cutaneous toxicity induced by radiotherapy. The hormone therapy given to patients undergoing radiotherapy did not result in increased breast cutaneous toxicity. Further analysis on a larger number of patients is necessary for definitive results.

Key words: breast cancer, cutaneous damage, radiotherapy.

Correspondence to: Vincenzo Ravo MD, UOC Radioterapia PO Ascalesi, Via Egiziaca a Forcella 31, 80131 Naples, Italy.
Tel +39-081-254-2177/2137/2185;
fax +39-081-5630660;
e-mail enzoravo@libero.it

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Introduction

External beam radiotherapy alone or in association with surgery and/or chemotherapy represents an integrating and irreplaceable part in the treatment of the breast cancer. In the last 30 years, technological improvements and greater precision in the delivery and in the dose distribution of radiotherapy have reduced the incidence of radio-induced complications[1]. However, a minimal part of patients may present an acute, subacute or chronic cutaneous damage of the healthy tissues involved in the radiation fields.

The prevention of acute effects on the skin and on the mucosae (cutaneous erythema, edema, pigmentation and/or mucositis)[2,3] is important. Topical treatments (creams, pastes or sprays) are used on the radio-treated surfaces both during the radiation treatment and several months after the end of the therapy.

Material and methods

From February 2009 to March 2010, in the Radiotherapy Department of P.O. Ascalesi, 100 consecutive patients affected by breast cancer and submitted to breast conservative treatment (quadrantectomy with or without homolateral axillary node dissection) were recruited. None of them was treated with prosthesis positioning. Of the 100 patients recruited, 52 underwent chemotherapy with a taxane and anthracycline prior to radiotherapy and 75 received hormone therapy during and after radiotherapy. Radiotherapy was delivered with a 3D conformational technique, and the total dose was 60 Gy in 30 fractions (2 Gy/die). All patients were treated with tangential beams using 6 Mv photons both for whole breast therapy and for tumor bed boost.

To prevent cutaneous effects induced by radiotherapy, all patients were submitted to therapy with one of the following topical treatments: 20 with pure vitamin E (Vea lipogel®), 20 with omega-3,6,9 (Quinovit®), 20 with betaglucan, sodium hyaluronate (Neoviderm®), 20 with *Vitis vinifera* A.s-I-M.t-O.dij (Ixoderm®), and 20 with natural triglycerides–fitosterols (Xderit®).

The topical treatment of irradiated skin began on the first day of radiotherapy and lasted until 3 months after the end of radiation treatment. Patients had to repeat the application of the cream every day (2-3 times/day). Moreover, during radiotherapy it was prohibited to use other types of creams or perfumes on the irradiated skin, and the patients were advised to wear preferably cotton clothes. From the beginning of the treatment, every week each patient was submitted to skin examination to evaluate cutaneous toxicity[4]. The evaluation was carried out using the RTOG scale[5] shown in Table 1. The skin side effects during treatments were scored by experienced radiation oncologists (i.e., with more than five years of clinical practice) who followed the patients during treatment in our department. It was only a clinical subjective analysis.

Table 1 - RTOG scale used

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	Light and/or painless erythema	Sensitive and/or intense erythema	Desquamation	Ulceration
No changes	Epilation	Desquamation	Widespread sweating	Hemorrhages
	Desquamation	Partial sweating	Marked edema	Necrosis
	Dryness	Moderate edema		

Cutaneous toxicity caused by radiations was estimated also during the follow-up, which was conducted approximately at 2-3 months after the end of radiation treatment in all the patients. All the patients who reported a G3 skin toxicity were treated locally with steroid products.

Results

All patients completed the radiotherapy, and G4 cutaneous toxicity was not observed in any of them. The complete results are shown in Table 2.

Of the 20 patients treated with pure vitamin E (Vea lipogel®), 3 developed G1 toxicity and 8 G2 toxicity during the radiation treatment; 5 patients of this subgroup also manifested G1 toxicity at the first follow-up.

Of the 20 patients treated with omega-3,6,9 (Quinovit®), 3 had G1 cutaneous toxicity, 9 G2 toxicity, and 5 G3 toxicity. Six of those who suffered cutaneous toxicity during the treatment also manifested G1 toxicity at the first follow-up.

Of the 20 patients treated with natural triglycerides-fitosterols-polyethyleneglycol (Xderit®), 4 had G1 toxicity, 8 G2 toxicity, and 5 G3 toxicity during the radiation treatment. Eight patients who suffered cutaneous toxicity during the treatment also showed G1 toxicity at the first follow-up.

Of the 20 patients treated with betaglucan, sodium hyaluronate (Neoviderm®), 6 showed G1 toxicity and 2 G2 toxicity during radiotherapy. Three patients who suffered cutaneous toxicity during the treatment also showed G1 toxicity at the first follow-up.

Table 2 - Toxicity, complete results

Cream	Toxicity G0	Toxicity G1	Toxicity G2	Toxicity G3	Anthracycline	Taxane therapy	Hormone
Pure vitamin E (Vea lipogel®)	9	3	8	0	6	4	15
Omega-3,6,9 (Quinovit®)	3	3	9	5	4	4	17
Natural triglycerides fitosterols (Xderit®)	3	4	8	5	7	7	14
Betaglucan, sodium hyaluronate (Neoviderm®)	12	6	2	0	6	4	15
Vitis vinifera A.s-I-M.t-O.dij (Ixoderm®)	11	8	1	0	4	3	14

Of the 20 patients treated with *Vitis vinifera* A.s-I-M.t-O.dij (Ixoderm®), 8 developed G1 toxicity and 1 G2 toxicity during radiation treatment. Of these patients, 5 manifested G1 toxicity also at the first follow-up. The results are shown in Table 3.

All patients who manifested G2 toxicity stopped the first topical treatment and were treated with cortisone creams[6], which determined a reduction in toxicity grade in 70% of the cases. Ten percent of the patients who manifested G3 cutaneous toxicity were treated with cortisone and healing creams. Three months after the end of radiotherapy, at the first follow-up visit, only 27% of the radiotherapy-treated patients still showed G1 cutaneous toxicity.

Of the 20 patients treated with pure vitamin E (Vea lipogel®), 6 had received chemotherapy with anthracyclines, 4 also with taxanes and 15 had received hormone therapy during the radiation treatment. Of the 6 patients treated with anthracyclines, 1 developed G1 and 2 G2 toxicity. Of the 4 treated also with taxanes, 1 developed G1 and 2 G2 toxicity. Of the 15 patients given hormone therapy, 4 developed G1 and 3 G2 toxicity.

Of the 20 patients treated with omega-3,6,9 (Quinovit®), 4 had been given chemotherapeutic treatment with anthracyclines, 4 also with taxanes, and 17 had received hormone therapy during the radiotherapy. Of the 8 patients treated with anthracyclines, 2 developed G1, 3 G2, and 1 G3 toxicity. Of the 5 patients treated with taxanes, 1 developed G1, 2 G2, and 1 G3 toxicity. Of the 17 patients given hormone therapy, 6 developed G1 and 4 G2 toxicity.

Of the 20 patients treated with natural triglyceridies, fitosterols, polyethylenglycol (Xderit®), 7 had received chemotherapy with anthracyclines, 7 also with taxanes, and 14 had received hormone therapy. Of the 7 patients treated with anthracyclines, 2 developed G1 and 2 G2 toxicity. Of the 7 treated with taxanes, 2 developed G1, 1 G2 toxicity, and 1 G3 toxicity. Of the 14 patients given hormone therapy, 5 developed G1, 4 G2, and 1 G3 toxicity.

Of the 20 patients treated with betaglucan, sodium hyaluronate (Neoviderm®), 6 had received chemotherapy with anthracyclines, 4 with taxanes, and 15 had received hormone treatment during the radiotherapy. Of the 6 patients treated with anthracyclines, 2 developed G1 and 1 G2 toxicity. The patient treated with taxanes developed G1 toxicity. Of the 15 patients given hormone therapy, 4 developed G1 and 2 G2 toxicity.

Of the 20 patients treated with *Vitis vinifera* A.s-I-M.t-O.dij (Ixoderm®), 4 had received chemotherapy with anthracyclines, 3 with taxanes and 14 had received the hormone treatment during radiotherapy. Of the 4 patients treated with anthracyclines, 3 developed G1 toxicity. Of the 4 treated with taxanes, 3 developed G1 toxicity. Of the 14 patients administered hormone therapy, 3 developed G1 and 1 G2 toxicity. The results are shown in Table 4.

Table 3 - Toxicity according to the product used

Cream	Toxicity G1	Toxicity G2	Toxicity G3
Pure vitamin E (Vea lipogel®)	5	0	0
Omega-3,6,9 (Quinovit®)	6	0	0
Natural triglycerides fitosterols (Xderit®)	8	0	0
Betaglucan, sodium hyaluronate (Neoviderm®)	3	0	0
Vitis vinifera A.s-I-M.t-O.dij (Ixoderm®)	5	0	0

Table 4 - Toxicity according to each product used and according to therapies received before (taxane, antracycline) or during (hormone therapy) radiotherapy treatment

Cream	Taxane	No.	Anthracycline		Hormone therapy	
Vea lipogel®	Tox G1	1	Tox G1	1	Tox G1	4
	Tox G2	2	Tox G2	2	Tox G2	3
	Tox G3	0	Tox G3	0	Tox G3	0
Quinovit®	Tox G1	1	Tox G1	2	Tox G1	6
	Tox G2	2	Tox G2	3	Tox G2	4
	Tox G3	1	Tox G3	1	Tox G3	0
Xderit®	Tox G1	2	Tox G1	2	Tox G1	5
	Tox G2	1	Tox G2	2	Tox G2	4
	Tox G3	1	Tox G3	0	Tox G3	1
Neoviderm®	Tox G1	1	Tox G1	2	Tox G1	4
	Tox G2	0	Tox G2	1	Tox G2	2
	Tox G3	0	Tox G3	0	Tox G3	0
Ixoderm®	Tox G1	3	Tox G1	3	Tox G1	3
	Tox G2	0	Tox G2	0	Tox G2	1
	Tox G3	0	Tox G3	0	Tox G3	0

Discussion

The breast cutaneous damage induced by radiation treatment on patients affected by breast cancer have often been evaluated. Some studies tried to evaluate the best topical treatment and the correlation between systemic therapy and skin radio-induced damage[7].

Moist desquamation, using current radiotherapy techniques, is a frequent consequence of radical doses of radiotherapy, and many products have been introduced in order to prevent such side effects[8-10]. In some cases, they did not work as expected.

Macmillan *et al.*[4] added to the knowledge on the risk factors for skin breakdown. These include concurrent chemotherapy, the use of a bolus, and smoking. Porock and Kristjanson[11] noted that much of the current research on radiation-induced skin reactions has focused on patients with breast cancer.

There are many factors that probably influence the appearance of side effects on the irradiated breasts. Bentzen *et al.*[5] found increased acute skin toxicity when patients received chemotherapy. Anthracyclines, pacli-

taxel and docetaxel are involved with a growing possibility of skin side effects[12,13].

In our experience, 10 patients (10%) reported a G3 toxicity without any specific correlation with the kind of chemotherapy received. All patients were treated at least one month after the end of chemotherapy and did not interrupt the radiotherapy. This may be the reason for the difference in cutaneous toxicity compared to the experience of Hanna *et al.*[12]

Hamilton *et al.*[7] reported that the erythema score might be influenced by the pre-treatment reflectance value, age, site and gender.

Turesson and Notter[14] found the peak acute reaction to be correlated with age, menopausal status, bilateral treatment and the type of radiation. The reasons for such variability in risk factors for acute skin reactions are not clear but could be related to differences in the study population or the small number of patients analyzed in the actual trial.

Roy *et al.*[15] showed that the use of soap and water on the treatment field during radiation therapy is a safe procedure. Washing the irradiated skin during the course of radiotherapy for breast cancer is not associated with increased skin toxicity and should not be discouraged. The concomitant chemotherapy and the presence of hot spots on dosimetry were significant prognostic factors for acute skin toxicity.

Fisher *et al.*[16] conducted the first study that evaluated trolamine (Biafine®) in preventing radiation-induced dermatitis in women who only underwent breast irradiation. In their phase III randomized study, the investigators found no overall difference between trolamine cream *versus* best supportive care in terms of prevention, time to, or duration of radiation-induced dermatitis. However, Trolamine significantly reduced skin toxicity after radiation therapy in large-breasted women and in nonsmoking women. The study of Szumacher *et al.*[17] differs from the trial of Fisher *et al.*[16] because their patients were younger and underwent more aggressive concomitant adjuvant chemotherapy in addition to radiotherapy.

Individuals treated with chemotherapy and radiotherapy are at increased risk for skin reactions because of the radiosensitizing properties of chemotherapeutic agents. As a consequence, their patients were more likely to develop skin toxicity than patients enrolled in the study of Fisher *et al.*[16] In conclusion, in the study of Szumacher *et al.*[17], most of the patients who underwent concomitant chemotherapy and radiotherapy for breast cancer developed grade 2 radiation dermatitis with the use trolamine cream. However, no treatment delays or interruptions were observed because of skin toxicity.

In our study, we did not observe any substantial difference in cutaneous tolerance to radiotherapy between patients previously treated with chemotherapy and those treated with surgery alone. The concomitant use of a hormone treatment also had an impact on the side effects of the skin. Our results may be influenced by the fact that we started a topical treatment systematically in all the treated patients from the first day of therapy.

Another current treatment policy in patients treated with radiotherapy is the prophylactic or therapeutic use of topical betamethasone. Omidvari *et al.*[18] treated 51 patients who underwent modified radical mastectomy for breast cancer and were going to receive radiotherapy, they were randomly assigned to receive topical 0.1% betamethasone, petrolatum or none during treatment. All patients developed some degree of acute radiation dermatitis, the frequency and severity of which increased with time and reached the maximum at the end of the seventh week for all groups. Patients receiving betamethasone had less severe acute radiation dermatitis than the other two groups throughout the course of the study, but the difference was significant only at the end of the third week ($P = 0.027$). The authors concluded that prophylactic and ongoing use of topical 0.1% betamethasone during chest wall radiotherapy for breast cancer delays the occurrence of side effects but does not prevent it.

Given these data and those deriving from our personal experience, we do not believe that the prophylactic use of topical corticosteroids is necessary for all patients. We reserved the use of corticosteroids only in the patient who during radiotherapy developed a G3 dermatitis while using the other prophylactic products that we prescribed.

One of the potential pitfalls in the evaluation of skin side effects during and after a radiotherapy treatment is that the clinical evaluation represents a subjective point of view about a clinical phenomenon. From the beginning of this year in our Department a new experience was started with a multidisciplinary approach about skin tolerance in patients treated with radiotherapy. Dermatologists and radiation oncologists perform a weekly evaluation of patients. Skin side effects during treatments are scored by the two specialists separately and then compared. Moreover, we began to determine skin hydration using a method known as corneometry[19,20]. Although it is a measure of the water content of the skin, it is only an indirect measure of barrier function. Nonetheless, it can be related to the extent of hydration under various physiologic conditions in response to injury, metabolic phenomena, or therapies such as radiotherapy. Since water loss through the skin normally occurs by passive diffusion through the epidermis, higher transepidermal water loss values indicate greater water loss and are consistent with increased damage of the barrier function of the stratum corneum such as may occur during irritant exposure, self-excoriation, or atopic dermatitis[20,21]. With this technique, we will try to give an objective measurement of the skin side effects of radiotherapy in patients treated for breast cancer.

Conclusions

Today there is growing interest in the treatment of cutaneous side effects of radiotherapy. Particularly women treated for breast cancer ask us not only the clinical resolution of their oncologic story but also a satisfactory esthetic condition. Our study highlights that hydrating creams play a fundamental role in preventing radio-induced cutaneous damage. In particular, betaglucan, sodium hyaluronate (Neoviderm®) and *Vitis vinifera* A.s-I-M.t-O.dij (Ixoderm®), of the five different topical treatments used, determined the best results to prevent cutaneous radio-induced damage. In our experience, chemotherapeutic treatment with taxanes and/or anthracyclines does not result in an increased breast cutaneous toxicity induced by radiotherapy. Moreover, hormone therapy performed by patients undergoing radiotherapy does not result in increased breast cutaneous toxicity, as reported in other experiences[22]. Further analysis and follow-up are necessary to give conclusive evaluations. We will also evaluate more patients, treating them with the five products tested from 2009 to 2010 and with other products that have been introduced in commerce. In the near future, we will also analyze the volumes of the treated breasts in order to find a correlation between breasts dimension and comparison of local side effects. Moreover, we will receive more data from the evaluation of skin hydration with the method known as corneometry, which we have introduced in the daily routine.

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