

Clinical evaluation of safety and efficacy of *Boswellia*-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial

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Abstract. – OBJECTIVE: Acute radiation erythema and other skin reactions are common adverse effects experienced by breast carcinoma patients undergoing radiotherapy treatment. Boswellic acids are pentacyclic triterpenes extracted from the resins of the tropical tree *Boswellia serrata* with strong anti-inflammatory properties. This study was designed to evaluate the safety and the efficacy of the application of a base cream containing boswellic acids in a proprietary formulation (Bosexil(R)) for the prevention and relief of radiation-induced adverse effects in breast cancer patients.

PATIENTS AND METHODS: The acute skin reactions were clinically evaluated by visual intensity and computer-assisted skin color analysis, and toxicity was assessed by the Radiation Therapy Oncology Group (RTOG) rating scale.

RESULTS: These findings indicate that the use of a boswellia-based cream is effective in reducing the use of topical corticosteroids and is able to reduce the grade of erythema and the skin superficial symptoms, being well tolerated by the patients.

CONCLUSIONS: Further studies comparing boswellia cream with other topical agents will be appropriate to confirm the effectiveness of this treatment for breast cancer patients under radiation therapy.

Key Words:

Boswellia serrata, Radiotherapy skin damage, Mammary carcinoma.

Introduction

The frequent adverse effects of adjuvant radiation therapy for the treatment of mammary carcinoma have been reduced by the advancements of therapeutic strategies and the improvements in

delivery made by the modern radiation technology¹. However, adjuvant radiotherapy for breast cancer still induces moderate-to-intense skin reaction in 85-95% of the patients, resulting in damage of basal epidermal cells, derma and vascular endothelial cells. The radiation-induced skin injury has been defined a “complex wound”, due to direct tissue damage and mediated by a sharp increase of free radicals, resulting in DNA damage and alteration of protein, lipids and carbohydrates. This is followed by skin cells death, which in turn causes an inflammatory process inside the tissue, affecting also the surrounding vascular microenvironment with recruitment of inflammatory cells. As a consequence, cutaneous vasodilation and edema occur, accompanied by the release of pro-inflammatory cytokines that trigger the inflammatory cascade. The clinical presentation is radiation dermatitis, classified according to the National Cancer Institute common toxicity criteria (version 3.0), from slight erythema (grade 1) to skin necrosis with ulceration of full-thickness dermis (grade 4)².

Slight acute radiation dermatitis is generally manageable with symptomatic treatments. However, when moist desquamation occurs (grades 2 and 3) topical agents based on some natural products may be needed, albeit with limited efficacy. The use of topical corticosteroids is controversial and at best they may ameliorate the dermatitis with no preventive effect²⁻³. Currently, there is no standard of care for prevention and control of radiation dermatitis.

The therapeutic use of preparations from the resin secreted by trees of the tropical *Boswellia* species was already known in Ancient Egypt and in Ayurvedic medicine several centuries BCE,

and it is currently exploited by traditional medicine in India and African countries for the treatment of a variety of diseases^{4,5}. There is *in vivo* evidence that alcoholic extracts of the resin of *Boswellia serrata* (*B. serrata*) exert anti-inflammatory and anti-phlogistic activities. These pharmacological effects are due to several boswellic acids (BAs), with steroid-like pentacyclic tri-terpene structure. In particular, β -boswellic acid (BA), acetyl- β -boswellic acid (ABA), 11-keto- β -boswellic acid (KBA), and 3-*O*-acetyl-11-keto- β -boswellic acid (AKBA) have been shown to inhibit the inflammatory process. The best characterized mechanism of action is 5-lipoxygenase inhibition. Other targets are pro-inflammatory cytokines, like interleukins and TNF- α , leukocyte elastase and leukotrienes as well⁴⁻⁶. Moreover, AKBA interferes with MAPK, NF- κ B and STAT3 pathways, with a potential anti-cancer effect, albeit to be fully elucidated yet⁷⁻⁸.

Moreover, it has been shown that extracts from *B. serrata* reduce redness and irritation of the skin, produce an even skin tone and have a soothing effect on irritated skin⁹. More recently, in a randomized double-blind, split-face study, a base cream containing BAs was successfully used to treat the clinical manifestations of photoaging on facial skin¹⁰.

In this study, we aimed at evaluating the efficacy of a *Boswellia*-based topical cream on the skin of breast cancer patients undergoing adjuvant radiotherapy, not only for their anti-inflammatory action in the acute phase, but also for a possible preventive treatment.

Patients and Methods

Patients

The parallel group, randomized, placebo-controlled study was conducted on 114 women subjected to adjuvant radiotherapy after surgery for mammary carcinoma, to compare a proprietary formulation of *Boswellia* cream in Phytosome(R) (Bosxil(R)) with base cream (placebo). There were no exclusion criteria for the participation in this study but radical mastectomy, because of the different body structure of the patients and the consequent different radiation techniques used. The patients randomized to *boswellia* cream were 55 (48.2%) versus 59 (51.8%) patients treated with base cream. Patients who received concomitant or previous chemotherapy were 17 (31%) in the group treated with *boswellia* cream

and 19 (32%) in the control group treated with base cream. The mean age of the sample was 58.2 ± 11.1 years (min = 32, max = 78) with a median of 58.5 years. The Chi-square test for independence of age and treatment revealed that the two parallel groups analyzed here were homogeneous ($p=0.768$). Similar results were obtained for skin and iris pigmentation, phototype and body mass index (BMI), evenly distributed between the two groups. All patients were overweight.

Radiation

Radiation therapy was delivered with 2 tangential fields to the chest wall with a photon beam energy of 6 Mv; in case of big breast we preferred a 4 fields with photon beam energy of 6 Mv and 18 Mv with differential weights, pair wise equal. All beams were shaped by Multi Leaf Collimators to minimize the amount of radiation absorbed by the cardiac and pulmonary parenchyma. Dynamic compensation wedges with adjustable angles and metacrylate compensation blocks were used to homogenize dose distribution in the irradiated volume and to reduce hot spots. The prescribed dose was 2 Gy per fraction and the clinical target volume was constantly in the range of 95% to 107%. All measures, including photographic evaluations, were performed after the patients received a dose/breast of 50 Gy, usually reached in 5 weeks of irradiation, 5 doses weekly. The treatments were completed by a wide "boost" on tumoral bed with external beams radiation therapy (EBRT) or brachytherapy.

Treatments

The cream (base cream placebo and *boswellia* cream 2%) was applied twice daily: immediately after radiation therapy and before bed-time in radiation therapy days, in the morning and at night in days with no radiotherapy administration. The application of the product immediately after radiation therapy was deemed necessary for relief of the acute inflammatory reaction occurring after radiation delivery. Among patients who received *boswellia* cream, a non-absorbed residue was reported and this was not always well tolerated. Moreover, a typical and marked fragrance was perceived as pleasant by some patients, while others regarded it as too intense.

Clinical Evaluation

The grade of intensity of the erythema developed after the radiation therapy was evaluated us-

ing the following visual grading scale: slight (slight redness, spotty, and diffuse), moderate (moderate and uniform redness), intense (intense redness)¹¹. Moreover, a more objective evaluation was based on the computer-assisted analysis of photographs of irradiated breast areas, compared with similar areas of non-irradiated normal breast, by digital evaluation of color magenta saturation (in percentage) of the two skin areas. We used a non-SLR camera, without flash and any additional filters; photographs were taken in ambient artificial light (examination rooms). The software used was Adobe Photoshop CS2 with image reader.

Statistical Analysis

Continuous variables (age, BMI, radiation) were analyzed by descriptive statistics: mean, standard deviation, median, percentiles, Student's *t* and Mann-Whitney U test for groups comparison. Categorical variables (skin and eye pigmentation, phototype, erythema scores) were analyzed by frequency table, percentage, Chi-square, Fisher exact test. In all tests $p < 0.05$ was considered statistically significant; $0.05 < p < 0.10$ values were considered as "close to significance". All analyses used the more conservative two-tail tests. All procedures were performed on iMac computer machines, by using SAS and XLSTAT softwares.

Results

Patients were clinically monitored during the treatment and all data on the administered supportive treatments were recorded.

Radiation erythema

The primary endpoint of this study was the intensity of erythema upon radiation therapy at the 50 Gy dose. The results in terms of visual intensity revealed that erythema was recorded as intense in a higher number of patients treated with base cream, compared with patients treated with boswellia cream (49.0% vs 22.0%). Slight and moderate intensity of erythema were scored more frequently in the boswellia cream group than in base cream group: 36.4% vs 20.3% and 41.8% vs 30.5%, respectively. The mode values of the intensity of erythema for these samples were: intense (70.7%) for the base cream group and slight (62.5%) for the boswellia cream group (Figure 1). According to the χ -square test analysis the differences measured in the grades of visual intensity of erythema were statistically significant ($p = 0.009$).

Trends of efficacy were also evident ($p = 0.018$) between the treatment with base and boswellia cream when concomitant chemotherapy was considered. When no concomitant chemotherapy was present, a higher proportion of patients treat-

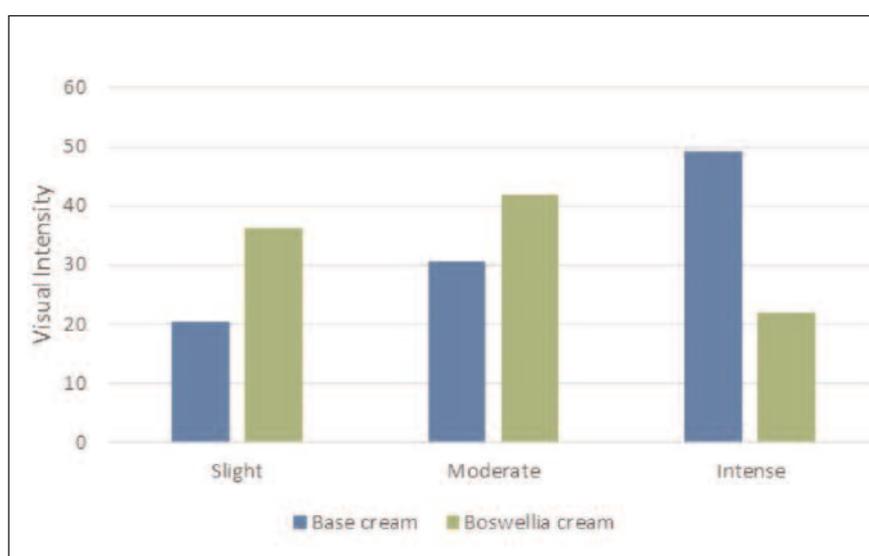


Figure 1. Visual intensity of erythema at 50 Gy.

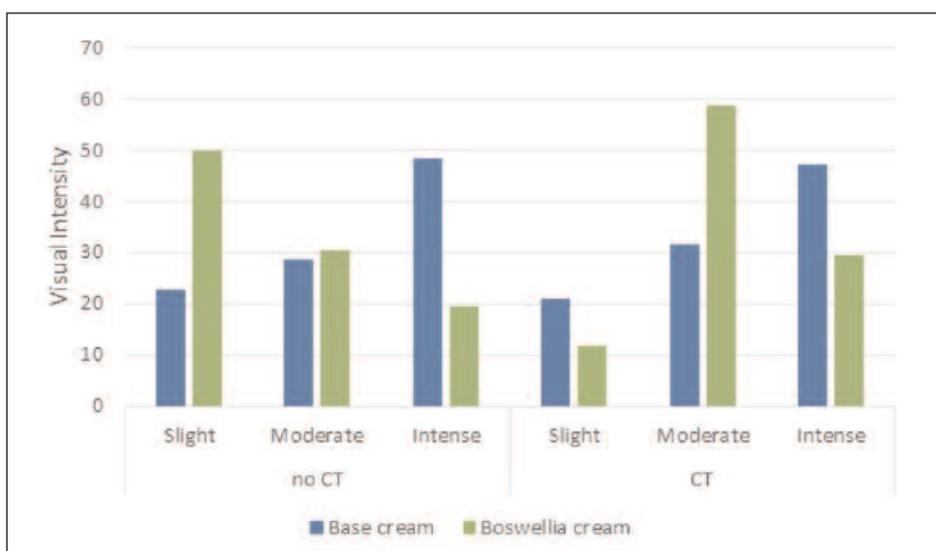


Figure 2. Visual intensity of erythema at 50 Gy: role of concomitant chemotherapy (CT).

ed with boswellia cream scored slight intensity of erythema compared to those of base cream group (50.0% vs 23.0%). Consistently, a lower fraction of boswellia cream group patients scored visual intensity of erythema as intense compared to patients of the base cream group (19.0% vs 48.6%) (Figure 2). Similarly, for patients receiving concomitant chemotherapy, a lower proportion (29.0% vs 47.0%) of intense erythema was observed in the group treated with boswellia cream, although statistical significance was not reached ($p=0.258$) (Figure 2).

To support the subjective evaluation of the degree of skin reaction based on grading of the visual intensity of the erythema, a more objective method of skin damage assessment was based on the notion that in the advanced phase of erythema the skin turns magenta-red or mauve in color¹². A computer-assisted evaluation allowed the digitalization of the intensity of magenta color in the picture photographs taken from the irradiated area of the breast where erythema developed after radiotherapy at 50 Gy. The intensity percentage value was compared with a similar area of the normal breast for each patient and a “delta” percentage difference was obtained. In patients of the boswellia cream group the mean value of skin damage is lower than that of the base cream group (10.1% vs 13.3%). The analysis performed with the non-parametric Mann-Whitney two-tailed test revealed that the probability of the differences between the two groups is statistically significant ($p = 0.009$).

Use of Cortisone

The use of topical hydrocortisone in the prophylaxis of radiation-induced dermatitis has been proposed over the last decades, although with controversial efficacy¹³. We aimed at verifying whether a different frequency in the use of this drug hormone occurred between the patients of base cream and boswellia cream groups. As shown in Table I, the percentage of patients receiving boswellia cream and using cortisone was lower than that of the base cream group using cortisone (25.0% vs 63.0%). Data analysis by χ^2 -square test revealed that the difference is statistically significant ($p < 0.0001$).

Toxicity

As a second endpoint the toxicity of radiotherapy was evaluated in the two groups of patients treated with base cream and with boswellia cream. The Radiation Therapy Oncology Group (RTOG) developed the Radiation Morbidity Scoring Criteria to classify the adverse events of radiotherapy¹⁴. RTOG score system has been widely employed in the past decades and is generally accepted by the medical community as a method to determine radiation-induced toxicity. Regarding the acute effects on the skin, the grading identifies the following degrees: 0 (no reaction); 1 (follicular, faint or bright erythema, epilation, dry desquamation, decreased sweating), 2 (tender or bright erythema, patchy moist desquamation, moderate edema); 3 (confluent, moist desquamation other

Table I. Use of cortisone upon adjuvant radiotherapy in patients receiving base cream or boswellia cream

Cortisone	Base cream		Boswellia cream	
	patients	%	patients	%
yes	37	62.71	14	25.45
no	22	37.29	41	74.55
	59	100.0	55	100.0

than skin folds, pitting edema); 4 (ulceration, hemorrhage, necrosis). The patients in our study were assessed by evaluation of the treated skin area every 20 Gy delivered, unless further visits on request or in case of specific problems. Acute toxicity was evaluated for the 50 Gy dose irradiated by external beams (some patients were irradiated with higher doses with brachytherapy techniques). As shown in Table II, the proportion of RTOG degree 1 of skin toxicity partly differed between the patients of base cream and boswellia cream groups (28.8% vs 45.5% respectively) and similar results were obtained for RTOG degree 2 (71.2% for base cream vs 54.6% for boswellia cream). The χ -square test analysis revealed that the difference was not statistically significant, although the results were close to significance ($p=0.066$).

Adverse effects in term of skin superficial symptoms (itching or burning sensation) were recorded, as were alterations of different epidermal areas (axilla, submammary groove, periareolar). Irrespective of the different treatments, total number of adverse effects were 50 (29 for the base cream group and 21 for the boswellia cream group). No significant differences were observed between the two groups regarding the epidermis alterations listed above, while a trend (although not statistically significant) was observed toward a reduction of the superficial symptoms in the boswellia cream group (10.0% for boswellia cream vs 22.5% for base cream group).

Discussion

Skin reactions during radiotherapy for breast carcinoma is the most common side effect, affecting the quality of life of these patients and potentially affecting the therapeutic program. Radiation-induced skin damage is mediated by free-radicals genotoxicity, followed by inflammatory response². To counteract the effects induced by radiation, breast intensity-modulated radiation therapy (IMRT) has been attempted¹ and for the relief of the acute inflammatory reaction several topical remedies have been tested, including a cream containing recombinant human epidermal growth factor (rhEGF)³. The anti-inflammatory properties of extracts from *Boswellia serrata* is well established⁴⁻⁶ and the application of a base cream containing boswellic acid has been proposed to counteract photo- and age-damaged skin^{10,15}.

In this study we tested the efficacy and safety of the application of a boswellia-based cream during adjuvant radiotherapy of patients with breast carcinoma. The treatment was well tolerated and no severe adverse effects were observed in the study population. As a primary endpoint we examined the intensity of the erythema upon radiotherapy at 50 Gy in the patients who received daily applications of boswellia cream compared with those who received the base cream as placebo. The intensity of erythema was evaluated by using a visual

Table II. Incidence of different RTOG score of skin toxicity by radiotherapy in patients receiving base cream or boswellia cream

RTOG score	Base cream		Boswellia cream	
	patients	%	patients	%
Degree 1	17	28.81	25	45.45
Degree 2	42	71.19	30	54.55
	59	100.0	55	100.0

RTOG: Radiation Therapy Oncology Group.

grading scale¹¹ and by a more objective computer-assisted analysis of the digitalization of the skin color associated to advanced stages of erythema, as a measure of the intensity of the process. The results of the two approaches were partially consistent. The analysis with the non parametric Mann-Whitney test on the skin color difference (“delta magenta” test) revealed a statistically significant increase in efficacy of the use of boswellia cream compared with placebo. Moreover the χ -square analysis of the data obtained with the visual intensity method revealed a significant difference between the two groups, suggesting a positive effect of the boswellia cream in reducing the intensity of the erythema (higher number of patients who scored slight erythema). The efficacy of the treatment with boswellia cream was further confirmed by the analysis of data on patients who were treated with concomitant chemotherapy. The use of topical corticosteroids in the control of radiation-induced dermatitis has been proposed for decades with debated efficacy^{13,16,17}. We aimed at verifying whether the use of boswellia cream could reduce the use of topical cortisone by patients undergoing radiotherapy. The results clearly indicate that a statistically significant lower percentage of patients receiving boswellia cream make use of topical corticosteroids, compared to those receiving the base cream.

According to the toxicity defined by RTOG criteria¹⁴ a difference “close to significant” was observed for degree 1 and 2 between the patients of the two groups. In fact, a trend of a lower incidence of skin superficial symptoms (itching, burning sensation) was observed in the boswellia cream group, suggesting that patients receiving boswellia cream may experience a reduced superficial toxicity in comparison with patients receiving placebo.

Conclusions

Our investigation on patients with breast carcinoma undergoing radiotherapy showed that a base cream containing boswellic acids (boswellia cream) could be safely applied to prevent or alleviate radiation-induced skin reactions. Future trials with robust sample size are warranted to confirm the effectiveness of a cream containing boswellic acids as a treatment for radiation skin reactions.

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Conflict of Interest

Stefano Togni and Giada Maramaldi are employee of Indena SpA. Luca Giacomelli is a consultant of Indena SpA. The other Authors declare that they have no conflicts of interest.

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