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Dermatoprotective Effect of Ocoxin Cream® in Cancer Patients Treated with Radiation Therapy. Case Series

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Abstract

Background: The effects of radiation therapy can impact patients' quality of life, leading to treatment interruptions and therefore sub-optimal outcomes. The main aim was to evaluate the preliminary effects of Ocoxin cream® in the prevention of radiation therapy. **Methods:** Fifty patients were enrolled in an observational, longitudinal, prospective, single-centre clinical trial in the Department of Radiation Therapy at the National Institute of Oncology and Radiobiology in Havana, Cuba. The Radiation Therapy Oncology Group (RTOG) toxicity criteria were used to classify the radiation therapy, and the Dermatology Life Quality Index (DLQI) instrument was used to assess quality of life. **Results:** Patients who met the inclusion criteria were enrolled consecutively and were treated with teletherapy using a ^{60}Co source with 1.25 MeV energy. 70.0% of the patients were head and neck cancer patients. No grade 3 - 4 radiation therapy was reported, nor were there any interruptions in radiation treatment due to skin toxicity. Radiation therapy was observed in only 14.0% of patients, and of these, only two patients developed grade 2 toxicity. The perception of quality of life before vs. after radiation therapy remained within an average range of "no effect" (at the start of radiation therapy) to "small effect" (at the end of radiation therapy). **Conclusions:** This clinical study is the first report of the use of Ocoxin cream® in cancer patients and demonstrates that it is able to prevent radiation therapy and reduce the severity of toxicity of treatment with ionising radiation.

Keywords

Dermatitis, Radiation Therapy, Ocoxin Cream®, Quality of Life

1. Introduction

Acute radiation dermatitis is one of the most common reactions to radiation therapy and usually appears within 90 days of exposure. The severity of the reaction varies from mild erythema to moist desquamation and ulceration [1]. The reaction usually begins 1 - 4 weeks after the start of radiation treatment and persists throughout the treatment period [2]. Ionising radiation is often used to treat various forms of cancer and it is estimated that 50% - 95% of these patients will develop some degree of radiation therapy [1] [3]. The effects of radiation damage can affect patients' quality of life and well-being, leading to a potentially harmful interruption of therapy and, consequently, inadequate treatment [4].

The pathogenesis of radiation therapy involves a combination of direct radiation damage and the subsequent inflammatory response, affecting the cellular components of the epidermis, dermis and vasculature [5]. The energy of the initial dose of ionising radiation during radiation therapy causes immediate tissue damage through the production of secondary electrons and reactive oxygen species (ROS) that attack cell structures. Each subsequent fraction of radiation leads to further recruitment of inflammatory cells [6] [7].

Management of radiation therapy can be challenging, so it is essential to be aware of the latest evidence in order to improve the efficacy and efficiency of care, improve treatment tolerability, reduce costs and improve patients' quality of life [8]. Advancements in radiation administration technology, such as intensity-modulated radiation therapy, can help minimise radiation-induced skin toxicity in certain tumour types, such as breast cancer [9]. Currently, recommendations are still limited and disparate because the studies conducted have a low level of evidence, with a predominance of case series and other studies with low methodological rigour and statistical power [10].

Data on the usefulness of natural products for the prevention and treatment of radiation dermatitis are even more limited and inconsistent [11].

Ocoxin cream®, a cosmetic product from Catalysis S.L., is indicated as a skin moisturiser and contains several molecules with recognised antioxidant, anti-inflammatory and healing action. In a clinical study on patients with multiple actinic keratosis, the use of Ocoxin cream® achieved a clinical response in 76% of patients, and complete remission demonstrated by histology in 75% of patients, as well as a significant recovery of elastosis and collagen formation, with no added toxicity [12].

The present investigation is based on a case report of patients treated with Ocoxin cream®, to evaluate its potential dermatoprotective effect in patients receiving

radiation treatment as monotherapy or in combination with chemotherapy.

2. Methods

2.1. Study Design

This was an observational, longitudinal and prospective study, which was carried out in the Department of Radiation therapy at the Institute of Oncology and Radiobiology (Havana, Cuba). Written informed consent was obtained from all participants, and the study was conducted in accordance with national good clinical practice guidelines for observational studies. The study protocol was approved by the research ethics committee of the Institute of Oncology and Radiobiology (prot. no. 58/2023). The aim of the study was to evaluate the preliminary effects of Ocoxin cream® in preventing radiation therapy in cancer patients receiving radiation treatment.

2.2. Study Population

Consecutively eligible participants (n = 50) were men and women over 18 years of age who met the following criteria: (a) with head and neck, breast, and gynaecological cancer sites; (b) receiving ^{60}Co radiation treatment as adjuvant or sole treatment; (c) who have not received prior radiation therapy or (d) who have conditions associated with radiation sensitivity such as xeroderma pigmentosum or ataxia telangiectasia; and (e) who have not used, and do not use, any pharmaceutical or natural products on the skin.

2.3. Procedure

Participants who met the inclusion criteria received Ocoxin cream® which was supplied by Catalysis S.L. (Madrid, Spain). The composition of Ocoxin cream® per 50 mL tube was: *Centella asiatica* Leaf Extract, *Pinus sylvestris* Bud Extract, Ammonium Glycyrrhizate, *Camellia sinensis* Leaf Extract, Ascorbic Acid, Zinc Sulfate, Pyridoxine HCL, Folic Acid, Ethylhexyl Methoxycinnamate, Steareth-2, Butyl Methoxydibenzoylmethane, Glycerin, Cetearyl Alcohol, Steareth-20, Cyclopentasiloxane, Titanium Dioxide (nano), Isohexadecane, Triethylhexanoin, Stearic Acid, Isopropyl Palmitate, Aluminum Stearate, Carbomer, Polyhydroxystearic Acid, Alumina, Sodium Lauroyl Lactylate, Ethylhexylglycerin, Ceramide NP, Ceramide AP, Ceramide EOP, Phytosphingosine, Cholesterol, Xanthan Gum, Sodium Hyaluronate, Sodium Hydroxide, Phenoxyethanol, Diazolidinyl Urea, Potassium Sorbate, Methylparaben, Propylparaben, Sodium Benzoate, Parfum (Geraniol, Hydroxycitronellal, Linalool, Coumarin, Hexyl Cinnamal, Limonene), and Aqua s.q.f.

After signing the consent form, the patient was instructed orally and in writing on the use of Ocoxin cream® (clean the area before use, and with clean hands, apply a thin layer of the cream twice a day to the area which will be subjected to radiation, indicated by the marking made by the doctor, and massage the area until the cream is completely absorbed). On radiation treatment days, the cream

was not applied prior to and for two hours following the sessions.

2.4. Endpoints

The primary endpoint was the incidence of adverse skin events secondary to radiation treatment. The secondary endpoints were: occurrence of temporary interruption of radiation therapy due to radiation therapy, occurrence of severe radiation therapy, and dermatological quality of life.

Weekly follow-up was conducted during the radiation treatment period to identify any adverse events, and for three months (day + 90) post-treatment. Between the weekly consultations, the team was available to answer patients' questions or address any other research-related concerns.

The RTOG toxicity criteria were used to classify these events. There are five categories, where 0: No change; 1: Erythema, depilation, dry desquamation; 2: Bright erythema, patchy moist desquamation, moderate oedema; 3: confluent moist desquamation, significant oedema; 4: Ulceration, haemorrhage, necrosis [13]. The highest degree of toxicity recorded by each patient was obtained for the assessment of toxicity. The effect was estimated as the proportion of patients with G3 or G4 radiation therapy and by the median treatment interruption time.

The validated Spanish version of the DLQI instrument was used to assess quality of life at the beginning and at the end of radiation treatment [14] [15]. This questionnaire is used in clinical practice and clinical trials to assess the impact of symptoms and treatment on patients' quality of life. The questionnaire consists of 10 questions with four answer options: "not at all", "a little", "a lot" or "very much", with corresponding scores of 0, 1, 2 and 3, respectively. The answer "not relevant" is scored as "0". The DLQI is calculated by adding up the scores from each question. The higher the score, the greater the deterioration in quality of life.

Data was collected from the baseline and final assessment forms. In the baseline assessment, before starting radiation therapy, data were collected on the following variables: socio-demographic (age, sex and skin phototype); lifestyle (alcohol consumption and smoking) and clinical and treatment variables (cancer diagnosis, total and daily irradiated dose in Grays [Gy] and concomitant chemotherapy). In the final assessment, performed at day + 90 after the start of radiation therapy, data were collected on the following variables: classification of radiation therapy according to the RTOG scale, temporary interruption of treatment with the number of days interrupted, fraction of radiation therapy and reason and adverse events, as well as the quality of life questionnaire (DLQI).

2.5. Statistical Analysis

The data analysis was descriptive. Qualitative variables were described using absolute and relative percentage frequencies. Pearson's chi-squared (X^2) statistical test was used as a method of analysis to assess the association between qualitative variables, and the non-parametric Wilcoxon test was used to compare quantitative variables shown as mean ± standard deviation. The statistical software SPSS

(Statistical Program for the Social Sciences Inc., Chicago, IL), version 25.0 for Windows® was used. A significance level of 0.05 was set for all tests.

3. Results

Fifty patients who met the inclusion criteria were enrolled consecutively and were treated with gamma radiation teletherapy using a ^{60}Co source with 1.25 MeV energy. The general characteristics are shown in Table 1. The median age was 63 years, 95% CI (58 - 64). There was a higher frequency of male patients (64%), and of head and neck cancer site (70.0%), while the most frequently represented skin phototypes were those classified as type II and IV; 28% and 38%, respectively. Concurrent chemotherapy was used in 24 patients with head and neck cancer, representing 66.7% of patients with this anatomical location, with cisplatin being the most commonly used antineoplastic drug.

Table 1. General patient Characteristics.

Characteristics		N	%
Age	(mean, 95% CI)	63.0, (58 - 64)	
Sex	Male	33	64.0
	Female	17	36.0
Location treated	**Head and neck**		
	Mesopharynx	16	32.0
	Oral cavity	12	24.0
	Larynx	7	14.0
	Parotid	1	2.0
	Breast	12	24.0
	Pelvis	2	4.0
Skin phototype	I	4	8.0
	II	14	28.0
	III	4	8.0
	IV	19	38.0
	V	4	8.0
	VI	5	10.0
Concurrent chemotherapy	Yes	24	48.0
	No	26	52.0
Total tumour dose (Gy), median 95% CI	Head and neck	66.00, (66 - 70)	
	Breast	40.05	
	Pelvis	50.00	

Radiation therapy was observed in only 14.0% of patients, and of these only two patients developed grade 2 toxicity. One of these patients had tumours located in

the mesopharynx (1), and the other was a woman with a gynaecological endometrial tumour. No grade 3 - 4 radiation therapy was reported, nor were there any interruptions in carrying out the radiation treatment due to skin toxicity. Two patients undergoing concurrent chemotherapy developed mucositis; grade 2 and grade 3 respectively. The latter voluntarily abandoned oncological treatment. One patient with an advanced tumour died during the follow-up period, after completion of radiation therapy, and this was assessed and concluded to be non-product-related toxicity. The incidence of toxicities was not correlated with the known risk factors, and as can be seen in Table 2, it is only statistically significant with regard to the anatomical location variable, in which proportionally, one of the two patients with pelvic radiation therapy presented radiation therapy, while despite while despite the number of patients who underwent head-and-neck radiation therapy being greater, only 11.1% reported such toxicity (4/36). Patients with skin phototypes II and III had a higher frequency of skin toxicities from radiation therapy, although there was no significant association (p = 0.182). A similar situation occurred with concurrent chemotherapy (p = 0.311).

Table 2. Distribution of skin toxicity grades (RTOG) and associated factors.

Factors		Toxicity				Total	p
		G0	G1	G2	G3-G4		
Age (years)	≤60	17	3	1	-	21	0.662
	>60	26	2	1	-	17	
Gender	Male	30	2	1	-	33	0.367
	Female	13	3	1	-	17	
Overweight/ Obese	Yes	15	2	0	-	17	0.570
	No	28	3	2	-	33	
Smoker	Yes	21	1	1	-	23	0.469
	No	22	4	1	-	27	
Tumour location	Head and neck	32	3	1	-	36	0.015
	Breast	10	2	0	-	12	
	Pelvis	1	0	1	-	2	
Total Radiation dose (Gy)	70	13	0	0	-	13	0.375
	66-69	17	1	1	-	16	
	50-65	6	2	1	-	9	
	40-49	10	2	0	-	12	
Concurrent chemotherapy	Yes	20	2	2	-	24	0.311
	No	23	3	0	-	26	
Skin phototype	Type I-III	17	3	2	-	22	0.182
	Type IV-VI	26	2	0	-	28	
	Total	43	5	2	0	50	

The perception of quality of life before vs. after radiation therapy remained within an average range of "no effect" (at the start of radiation therapy) to "small effect" (at the end of radiation therapy) in this case series (Table 3). This change in perception is statistically significant according to the Wilcoxon test (p = 0.021). However, no patient reached a score of "extremely large effect" on the patient's life.

Table 3. Dermatological quality of life assessment (DLQI).

	Items	Start of RT	End of RT	p
		Mean ± SD	Mean ± SD	
1	Itching, pain, stinging.	0.194 ± 0.328	0.625 ± 0.696	<0.001
2	Discomfort or self-consciousness due to skin problems.	0.267 ± 0.370	0.424 ± 0.574	0.173
3	Issues going shopping, doing activities at home.	0.104 ± 0.471	0.310 ± 0.668	0.193
4	Issues choosing what clothes to wear.	0.062 ± 0.433	0.292 ± 0.743	0.082
5	Issues with any social or recreational activities.	0.128 ± 0.267	0.226 ± 0.444	0.211
6	Difficulties in doing sport.	0.021 ± 0.144	0.125 ± 0.334	0.059
7	Completely unable to work or study.	0.406 ± 0.616	0.395 ± 0.564	0.945
8	Difficulties with partner, close friends or family.	0.111 ± 0.353	0.111 ± 0.366	0.874
9	Difficulties with sex life.	0.104 ± 0.371	0.187 ± 0.420	0.193
10	Difficulties taking up too much time or making a mess of the home.	0.135 ± 0.533	0.229 ± 0.515	0.186
	Overall	1.540 ± 2.625	2.865 ± 3.665	0.021

Legend: RT: radiation therapy; SD: standard deviation; p: statistical significance.

4. Discussion

The use of ionising radiation in cancer treatment has had an impact on disease control, symptom relief and survival. Skin toxicities are very common side effects of external radiation therapy and have a variable impact in terms of severity, course of treatment and prognosis, which can interfere with the radiation dose and treatment compliance [5] [16]. The mechanism of ionising radiation-induced skin toxicity has been attributed to apoptosis, mitotic catastrophe and necrosis, leading to the development of skin reactions such as inflammation, which occur a few weeks after radiation therapy. It is therefore imperative to protect this important organ from the harmful effects of ionising radiation [17].

The most represented anatomical locations in this case series were head and neck and breast, in which the above effects were demonstrated. Head and neck cancer is one of the most common cancers worldwide, and its control and curability remain a challenge despite advancements including the use of cisplatin as a

radiosensitiser in combination with radiation therapy, the use of immunotherapy, and p16 protein and HPV expression levels as prognostic predictors [18]. In women, breast cancer is the most common cancer globally, and depending on the stage at diagnosis and molecular phenotype, most patients receive adjuvant radiation therapy after surgery, with an impact on controlling local relapse and improved survival [19].

Patients with head and neck cancer have a higher incidence of radiation therapy, with greater severity and intensity, than patients with other tumour sites. Some reports agree that they occur in 80% - 100% of all treated patients, while in other locations these figures are lower [20] [21]. Several factors are associated with the high incidence of skin toxicity from radiation therapy in patients with head and neck cancer, including ultraviolet radiation exposure, air pollution, smoking and other factors that alter the skin barrier function [20]. Radiation treatment causes less radiation therapy in breast cancer, but its incidence is not negligible and still remains very high (50% - 76%) [20] [22]. Based on the data collected in this report, the use of Ocoxin cream® reduces the incidence of this skin toxicity by 60-80% in patients with cancer at these anatomical sites. However, no correlation was observed between radiation therapy and the vast majority of known risk factors, which may in part be explained by the size of the sample selected. In the case of gynaecological tumours, as the area to be irradiated is much larger than the previous sites discussed, consideration should be given to intensifying the dose of the product with a view to increasing its effect. The number of cases treated and included in this series is too small to reach conclusions in this respect.

When radiation therapy occurs in a patient, it can have significant repercussions on many levels. Local discomfort (itching, burning), the appearance of skin lesions, the psychological impact in terms of aesthetics and body image, together with the resulting delays in treatment and reduced tumour control, all result in a real decline in quality of life [8]. Assessment of dermatological quality of life with the DLQI instrument in patients treated with radiation therapy has been performed in some clinical studies and has proven useful in these studies [23] [24]. As treatment progresses, and radiation therapy starts to appear or worsens, there is a tendency for DLQI items to be scored more highly. A study carried out in Brazil in patients with breast cancer corroborates the above, where there was a tendency for the severity of signs and symptoms such as sensitivity, discomfort or pain, visualisation, burning and heat, dry and moist desquamation, to increase. These signs and symptoms could have had an impact on quality of life and been reflected in other aspects, such as shopping or going out ($p = 0.0020$), social or leisure activities ($p = 0.0420$) [25].

In our series, the DLQI results show that patients' overall quality of life at the end of the study was comparable to that at baseline, classifying it as having a small or limited effect [26]. With regard to the sub-scales, those with the highest scores were related to symptoms (items 1 and 2) and daily activities (items 3 and 4), with scores increasing by more than three times compared to the baseline assessment.

Only item 1 was statistically significant and directly related to subjective manifestations of symptoms, but these did not translate into cutaneous signs that would change the radiation therapy classification. The topical use of Ocoxin cream® appears to improve skin comfort for patients, thus allowing them to maintain a stable level of quality of life and limit the impact of radiation therapy.

The preventive use of dermal products reduces the incidence of skin side effects. Many products have been studied, including aloe vera, calendula, corticosteroids, hyaluronic acid, urea, topical sucralfate, trolamine, granulocyte and macrophage stimulating factors, various dressings and barrier creams [27] [28]. Most interventions are not recommended due to low quality of evidence, lack of supporting evidence, or contradictory findings in multiple trials, and moreover, not all of them present an evidence level in the prevention of skin toxicity, but rather in the specific treatment of radiation therapy [29]-[31]. The strongest consensus among guidelines is on the use of topical corticosteroids, and washing with soap and water [30].

The use of corticosteroids is based on their anti-inflammatory effect through vasoconstriction, reduction of capillary permeability and inhibition of leukocyte proliferation and migration. This inflammatory action helps to prevent and reduce the symptoms of skin inflammation and improves quality of life. However, corticosteroids also have adverse effects on the skin and body, such as glaucoma, Cushing's syndrome, hypertension, hirsutism and hyperpigmentation. Additionally, treatment with corticosteroids should not exceed 12 weeks, as this may increase the incidence of adverse reactions, such as hirsutism and fungal skin infections [32] [33].

Creams are the topical products most often recommended in the literature for use in the prevention of radiation therapy and are intended to treat erythema and limit dry desquamation, minimise insensible water loss, reduce pain and prevent progression to moist desquamation [34]. During radiation treatment, hypoxia is induced by damage to the vascular endothelium, positively regulating transforming growth factor (TGF)-b, and leads to increased fibrosis and hypoxia. This in turn causes generation of ROS, which dramatically increases and overwhelms the body's protective antioxidant system, and promotes the production of inflammatory cytokines in the skin. These activating signals give rise to a cascade of cytokines and chemokines (*i.e.* interleukin [IL]-1a, IL-1b, tumour necrosis factor [TNF]-a, IL-6, IL-8, C-C motif chemokine ligand [CCL]-4, C-X-C motif chemokine ligand [CXCL]-10 and CCL2) which in turn lead to skin fibrosis, the production of matrix metalloproteases that degrade dermal components and the basal cell layer, and act on vascular endothelial cells to positively regulate adhesion molecules (*i.e.* intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1 and E-selectin) [35] [36].

Although controversial, the use of antioxidants in cancer patients may counteract or at least minimise the toxic effects of oxidative stress on normal cells [37]. The anti-tumour effects of Ocoxin oral solution have been confirmed in several preclinical studies. In animal models, synergy with chemotherapy and targeted

therapies has been observed in decreasing anti-tumour cell proliferation, while in clinical trials, quality of life is significantly improved, with better tolerability to conventional therapies and reduced adverse effects [38] [39].

The ingredients in Ocoxin cream® inhibit oxidative stress at the keratinocyte level, reduce the inflammation-related mechanisms, and thus modify the cutaneous signs of skin alteration secondary to ionising radiation. Three of the four plant extracts (glycyrrhizic acid, epigallocatechin-3-gallate (EGCG), and *Pinus sylvestris* bud extract), as well as ascorbic acid, help to control oxidative damage to the skin [40]-[43]. Glycyrrhizic acid promotes the control of inflammation by reducing serum levels of inflammatory cytokines and high mobility group box 1 (HMGB1) following radiation treatment [44]. EGCG suppresses gene and/or protein expression of inflammatory cytokines and inflammation-related enzymes [45]. The high level of asiaticosides and madecassosides in *Centella asiatica* leaf extract, along with *Pinus sylvestris* bud extract and zinc sulphate, help to control inflammation and skin healing processes, and are therefore widely used in the recovery of burns, wounds, keloids, and stretch marks [42] [46] [47]. Ceramides are part of the skin's physical defence barrier, and help to maintain skin hydration and protection, while hyaluronic acid promotes skin hydration by helping to penetrate into the deeper layers and attracting water molecules [48] [49]. Sodium lauroyl lactate also contributes to skin hydration and the integrity of the skin's physical defence barrier [48].

5. Conclusion

In this case series of patients who received Ocoxin cream®, there was a low frequency of skin toxicities, with no interruption of radiation therapy treatment and a small change in the perception of dermatological quality of life. This was probably due to the restoration of the antioxidant balance of irradiated skin tissues, given the potential protective effect of Ocoxin cream® against oxidative damage induced by ionising radiation on the skin. This study could serve as a basis for future placebo-controlled clinical trials that would provide the further scientific evidence needed on the efficacy and safety of a cream containing natural products and which could demonstrate equal or superior efficacy to a topical corticosteroid in the prevention of radiation therapy, without the side effects associated with corticosteroids.

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Conflicts of Interest

JLSG is a medical consultant for Catalysis S.L. The other authors declare that they have no conflict of interest with regard to the publication of this article.

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Appendix

Dermatology Life Quality Index (DLQI).

Question	Answer			
1. Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
3. Over the last week, how much as your skin interfered with you going shopping or looking after your home or garden?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
4. Over the last week, how much as your skin influenced the clothes you wear?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
5. Over the last week, how much as your skin affected any social or leisure activities?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
6. Over the last week, how much has your skin made it difficult for you to do any sport?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
7. Over the last week, has your skin prevented you from working or studying? If "No", over the last week how much has your skin been a problem at work or studying?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
9. Over the last week, how much has your skin caused any sexual difficulties?	Very much ☐	A little ☐	A lot ☐	Not at all ☐
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much ☐	A little ☐	A lot ☐	Not at all ☐