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Electrochemotherapy, a Local Treatment for Squamous Cell Carcinoma in Patients with Epidermolysis Bullosa

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Abstract

Epidermolysis Bullosa is a rare heterogeneous group of diseases caused by mutations in various skin structural proteins characterized by varying degrees of skin fragility, blisters and impaired wound healing. It is classified based on the ultrastructural levels of skin cleavage-simplex, junctional, dystrophic and Kindler Syndrome. Recently, there has been considerable progress in the management of these patients, emphasizing a multidisciplinary approach. However, Squamous Cell Carcinoma (SCC) is still the most severe complication, with a cumulative risk of 90.1% by age 55. SCC is the most common cause of death in these patients, particularly in Recessive Dystrophic Epidermolysis Bullosa (RDEB).

To date, the first line of treatment is surgery, even though the risk of recurrence is still high, even with wide excisions with negative margins. Radiotherapy and systemic therapy have been avoided due to its skin toxicity, but it can still be an option as palliative therapy.

Recently, Electrochemotherapy (ECT) has been proposed as a potential treatment; however there is not enough date to support its efficiency.

We report five patients with SCC in RDEB who were treated with ECT using bleomycin intravenously. These patients were evaluated after four and eight weeks and all showed an objective response. Four patients had a complete response. The treatment was well tolerated, with mild adverse effects, such as local pain, oedema, and erythema and skin ulceration.

Our results demonstrate that ECT is a potential treatment for SCC in patients with RDEB. However, there is still not enough data to confirm its evidence.

Keywords: Epidermolysis bullosa; Electroporation; Chemotherapy; Skin cancer

Introduction

Epidermolysis Bullosa (EB) is a rare heterogeneous group of diseases caused by mutations in various skin structural proteins and characterized by varying degrees of skin fragility, blisters and impaired wound healing [1-4].

The classification of inherited EB has recently been updated and four major types can be identified based on the ultrastructural levels of skin cleavage -simplex, junctional, dystrophic and Kindler Syndrome. Dystrophic EB results from a mutation in the gene COL7A1 that encodes type VII collagen, which is the major component of anchoring fibrils [2].

There has been considerable progress in the management of these patients, emphasizing a multidisciplinary approach [1]. However, Squamous Cell Carcinoma (SCC) is still the most severe complication, particularly those with Recessive Dystrophic Epidermolysis Bullosa (RDEB) [1,3-5]. The cumulative risk of developing the first SCC is of 7.5% by the age 20, which rapidly increases thereafter, with a risk of 67.8%, 73.4%, 80.2% and 90.1% by age 35, 40, 45 and 55 years, respectively [4].

The majority of SCCs are histologically well differentiated. Nonetheless, they have an aggressive course with high risk of local recurrence and metastization, which becomes the major cause of death in patients with RDEB, with a cumulative risk of death is 87.3% by age 45.3 years Furthermore, more than 60% of RDEB patients develop multiple primary SCC, which will influence the approach and the outcome [1,3,4] The appearance of SCCs in those patients is sometimes difficult to distinguished from chronic ulceration and scaring widely seen in EB. Therefore, the threshold to biopsy should be low [1].

To date, the first line of treatment for SCCs is surgery, despite the risk of recurrence being still high, even with complete resections [3,6]. Moreover, these patients do not heal easily due to the recurrent blistering and ulceration and also because of their poor nutritional status, resulting in a high morbidity [7].

Radiotherapy and systemic therapy are only considered as palliative therapy, due to its skin toxicity [8,9]. Recently, Electrochemotherapy (ECT) has been proposed as a potential treatment [5,6]. ECT is a local treatment in which the administration of a non-permeant

chemotherapeutic drug, such as bleomycin or cysplatin, in low-dose is followed by local application of electric pulses transiently permeabilizing the cell membranes, increasing the effectiveness of the drug and reducing its side effects (Figure 1) [10-14].

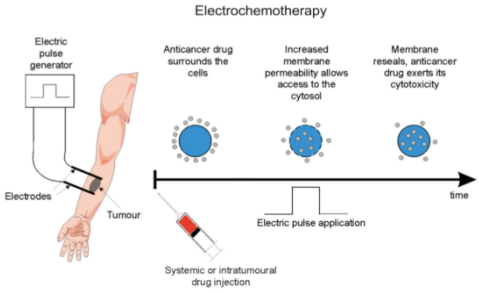

Figure 1: Principle of Electrochemotherapy.

ECT has been considered an effective treatment for cutaneous and subcutaneous tumours [13], such as SCC, in carefully selected cases [15] Therefore, ECT has also been proposed as a local treatment for patients with RDEB (grade 3D) [5], with three cases reported in the literature with a high overall response [6]. It is usually well tolerated, with only transient mild adverse effects, such as local pain, oedema, and erythema and skin ulceration. This approach also affects the quality of life, with control of bleeding and odor from fungating tumours [15].

The objective of this study is to evaluate the potential use of ECT as a local treatment for patients with RDEB with SCC, allowing the possibility to avoid surgical excision and its associated morbidity.

Material and Methods

Retrospective study which included patients with the diagnose of RDEB that undergone ECT for treatment of SCC at the Portuguese Oncology Institute of Lisbon during the period from May 2011 to October 2017. All patients were referred to our institution from a Genodermatosis treating group of a different medical centre after the diagnose of the SCC confirmed by biopsy. They were first evaluated at a multidisciplinary group meeting dedicated to skin cancer treatment, and then referred to the surgical department for treatment.

The ECT sessions were performed following the European Standard Operating Procedures for ECT (ESOPE) [12]. We used the CliniporatorTM 1 device (Figure 2) with type three electrodes (hexagonal N-20-HG). Bleomycin was administrated intravenously during two minutes at a dose of 15000 UI/m^2, followed by electric pulses eight minutes later, with a maximum duration of treatment of twenty minutes.

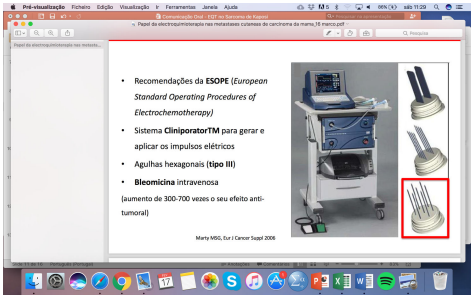

Figure 2: Cliniporator TM 1 device-produced by IGEA®.

All five patients were evaluated four and eight weeks later. The lesions were carefully examined and measured to determine the response to treatment. The side effects of this procedure were registered during the follow up period, which include local pain, erythema and transitory skin ulceration.

According to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [16], we defined as complete response the absence of palpable or measurable tumour, and as partial response the decrease of at least 30% of tumour volume.

Results

We report eight sessions of ECT in five patients with RDEB for treatment of SCC in the Portuguese Oncology Institute of Lisbon during the period of study. The clinical features of the treated patients are described below (Table 1). After a follow up of eight weeks, these patients continued their evaluation with Dermatology, with the Genodermatosis treating group.

Number of Patient	Sex	Age (years)	Site of SCC	Number of ECT sessions	Dose of Bleomycin iv (15.000 UI/m^2)	Side effects	Response
1	M	38	Left arm	4	22.5	Intense pain, ulceration, erythema	CR
			Right knee				
			Right foot				
			Left foot				
2	F	37	Right leg	1	18.585	Pain, ulceration, erythema	PR
			Right arm				
3	M	38	Right knee	1	25.5	Ulceration, erythema	CR
4	M	45	Left hand	1	23.85	Pain	CR

5	F	35	Right leg	1	20.7	Ulceration	CR
CR-Complete Response; PR-Parcial Response							

Table 1: Recessive Dystrophic Epidermolysis Bullosa patients with multiple squamous cell carcinomas treated with electrochemotherapy, clinical features.

Patient-1

A 38 year old Caucasian male with multiple SCC in different sites that had previous surgical excisions, Due to the recurrence of lesions and the morbidity associated to poor healing after surgery, this patient was proposed for ECT of the new lesions. He was treated with four sessions of Electrochemotherapy during a period of two years. After the final session, a complete response to treatment was obtained and a biopsy confirmed the complete healing of the lesions.

Patient-2

A 37 year old Caucasian female with SCC on the right leg and arm who undergone one session of ECT. After four weeks of follow up she presents a good objective response. After the final evaluation she demonstrated a partial response and was proposed to a second session. However, the patient denied more sessions and decided for amputation.

Patient-3

A 38 year old Caucasian male with recurrent SCC in the right knee who had two surgical excisions before, one of which was incomplete with positive margins. After the second surgery, due to his skin disorder and the location of the SCC, surgical excision of the new lesion was associated with high morbidity. To avoid amputation of the limb, he was proposed for one session of ECT. The response was complete, with complete skin healing after eight weeks of follow-up. The patient had only erythema and ulceration during the first four weeks which resolved completely (Figure 3).

Figure 3: Squamous cell carcinoma of the right knee before ECT session-Patient 3 (a), Edema and erythema one week after treatment (b), Ulceration and initial healing four weeks follow-up (c), Healing of the skin after eight weeks (d).

Patient-4

A 45 year old Caucasian male with local SCC of the left hand who undergo surgical excision with incomplete positive margins. After multidisciplinary discussion he was proposed to one session of ECT of the residual SCC. After eight weeks of follow up the response was complete. The patient had only local pain during the first four weeks with complete resolution.

Patient-5

A 35 year old Caucasian female with a first SCC located in the right leg, without previous surgical excisions. She was proposed for ECT as a first line of treatment. The response after eight weeks was complete with only mild adverse effects, such as local ulceration during the first four weeks, with complete healing (Figure 4).

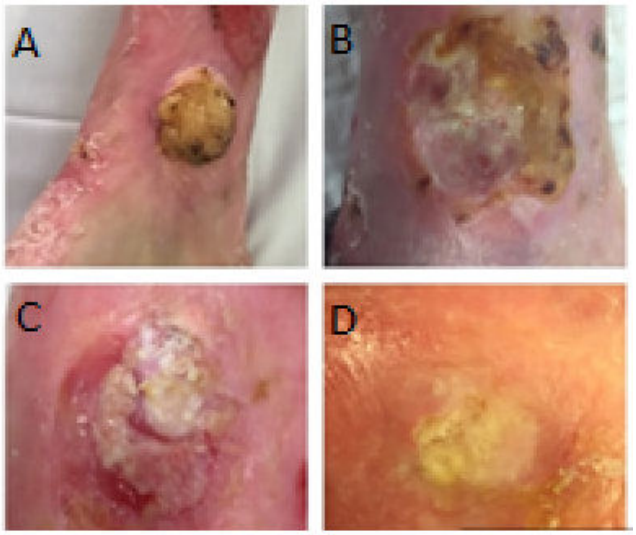

Figure 4: Squamous cell carcinoma of the right leg before ECT session-Patient 5 Ulcerations one week after treatment (b), Ulceration and initial healing four weeks follow-up (c), Healing of the skin after eight weeks (d).

Discussion

The standard treatment of local SCCs is surgery, whether it is low or high-risk tumours. According to the latest NCCN guidelines, the primary treatment for skin SCC is curettage or standard excision. Radiotherapy and systemic therapy are usually reserved for non-surgical candidates. ECT has been recently proposed as a potential treatment for selected patients when first line options are not available. It is an effective treatment for local control of the disease with low adverse effects and toxicity [13].

In patients with RDEB, the treatment options for SCC are similar as for patients without this disease. The first line of treatment is surgery, however due to their healing disorder and low nutritional status, other

treatment options should be considered. Radiotherapy and systemic therapy have been avoided due to its skin toxicity, but it can still be an option as palliative therapy. ECT has been proposed as a new local treatment due to its effectiveness and low skin toxicity. This procedure facilitates the drug delivery into the cells by combining the administration of non-permeant chemotherapeutic drugs with application of electric pulses to the tumours. Therefore, it enhances drug delivery and potentiates the local chemotherapeutic drug effectiveness at the site of cell permeabilization by electric pulses. The tissues that are unexposed to electric pulses are not affected, which results in low toxicity.

We report five patients with SCC in RDEB who were treated with ECT using bleomycin intravenously. These patients were evaluated after four and eight weeks and all showed an objective response, with reduced tumour volume. Four patients had a complete response. The treatment was well tolerated, with only mild adverse effects, such as local pain, oedema, and erythema and skin ulceration. These patients were submitted to surgical excision first, with local recurrence of the disease associated to high morbidity with poor skin healing.

Despite the fact that this is a local treatment with no impact in the control of the progression of the disease, it is a treatment that can be repeated whenever necessary with few complications associated and no evident contraindications.

There are only three cases described in the literature that evaluated ECT as local treatment for SCC in patients with RDEB, with a high response rate, which was well tolerated with low adverse effects.

The results we had can support those reports and reinforces the effectiveness of ECT in EBDR patients with SCC.

Conclusion

SCC is a major cause of morbidity and mortality in patients with EB. To date, the standard treatment is surgery; however the morbidity associated is considerable high. ECT has been proposed as a local treatment for SCC in selected patients, such as in these patients with RDEB. This treatment has been used for cutaneous and subcutaneous tumours with high overall effectiveness. It has been routinely used due to its effectiveness but also because of its safety, limited toxicity, cost-effectiveness, and organ-sparing effect and suitable for repetitive treatment.

The five cases we report showed an objective response, with reduced tumour volume and four patients had a complete response. Our results demonstrate that ECT can be proposed as a local treatment for SCC in patients with RDEB. These results are supported by the cases reported previously. Nonetheless; there is still not enough data to confirm its evidence.

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