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Unique Clinical Features of Curaderm when Treating Skin Cancers

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Abstract

Basal cell carcinoma is the most common form of skin cancer and the most frequently occurring form of all cancers. Conventional treatments to remove or destroy basal cell carcinoma are indiscriminate and also remove or destroy normal skin cells resulting in compromised cosmetic outcomes. Consequences of these treatments include body-image issues, anxiety, post-traumatic stress disorder, depression, and poorer quality of social and family life. A progressive topical cream formulation, Curaderm, containing the natural BEC glycoalkaloids, have shown to have advantages over conventional treatments. However, comprehensive clinical features of the skin cancer lesions during treatment with Curaderm have to date not been reported. This report shows that using unpublished data from a large number of patients with varying sizes, types and locations of basal cell carcinomas when treated with Curaderm in a phase 3 trial, an initial increase in size of the lesions occur, followed by a reverse course, leading to complete removal of the skin cancer. The specificity and mode of action of Curaderm explains the superior cosmetic outcomes when compared with conventional therapies.

Keywords

Curaderm, Skin Cancer, Basal Cell Carcinoma, BEC, Glycoalkaloids, Conventional Treatments

1. Introduction

The most common forms of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), collectively known as nonmelanoma skin cancer (NMSC), and melanoma which are named after the three main types of cells located in the uppermost layers of the skin.

Basal cells are formed at a deeper level and migrate upwards to eventually re-

place the surface squamous cells.

Squamous cells are flat cells on the surface of the skin epidermis that are constantly wearing off and are shed from the skin. More than 1 million cells are shed from the skin daily. Melanocytes manufacture the pigment melanin that gives the skin its colour.

Other more rare forms of skin cancers are Merkel cell carcinoma, Kaposi sarcoma and Skin lymphoma. Actinic keratosis (AK) is a precancerous growth that can turn into an SCC.

Melanoma accounts for only about 1 percent whereas, SCCs for about 20 percent and BCCs for about 80 percent of all skin cancers.

The primary causes of skin cancer and AK are overexposure to sunlight. The DNA of an affected skin cell is harmed by the sun's ultraviolet (UV) rays that can result in skin cancer. In the United States of America (USA), skin cancer diagnoses outnumber those of all other cancers combined.

In 2012, more than 5.4 million cases of nonmelanoma skin cancers (NMSC) were treated. By the age of 70 years, at least one in five Americans and one in two Australians will have skin cancer. Every day, more than 10,000 Americans are diagnosed with skin cancer. Every hour, more than two people pass away from skin cancer. AK affects more than 58 million people in the USA. It is estimated that the yearly cost of treating skin cancers in the USA is over $8 billion, of which over $3 billion goes toward melanoma and $5 billion goes toward NMSC.

Methods of treating skin cancer and AK vary according to the form they take, how large they have grown, how long they have been present and where the lesion is located.

Excision surgery is used to treat BCCs, SCCs and melanomas by numbing the skin with a local anaesthetic and cutting away the cancerous tissue. A margin of surrounding normal tissue is also cut away to ensure the cancer is completely removed. The effect of surgery can be slow healing and may require a skin flap or skin graft.

Mohs Micrographic Surgery, the current "gold-standard" surgical approach involves an outpatient procedure using lateral incisions to remove thin horizontal slices of tissue that are immediately placed under a microscope and examined to determine if the bottom and margins of the slice contain cancer cells. Once a slice reveals that the bottom and margins are cancer-free, the wound is stitched closed.

Hedgehog pathway inhibitors are indicated for BCC in adults with advanced, or recurred tumour following surgery or radiation therapy.

Laser therapy uses light beams of various sources to burn away AK and small superficial BCCs and SCCs.

Cryotherapy uses liquid nitrogen that is applied to the lesion to freeze AK, BCCs and SCCs, sometimes more than once, during a single office visit. When the skin thaws, it swells, blisters and oozes, and may take several months to heal.

Curettage and electrodesiccation is another inpatient procedure, where the

doctor scrapes away the cancer, using a scoop-like instrument, and then applies electrified needles to the area to destroy any remaining cancer cells. This procedure often requires repeats during the same office visit and is usually confined to BCCs and SCCs.

Photodynamic therapy (PDT) treats AK, small BCCs and SCCs by placing a topically applied liquid drug on affected areas where it interacts with tumour cells and over time, makes them hypersensitive to certain wavelengths of light, which are then applied to kill the cells. This procedure causes redness and swelling, leaving the patient's skin highly sensitive to sunlight.

Chemical peels with trichloroacetic acid (TCA) treat epidermal lesions such as AK and superficial SCCs.

Topical chemotherapy 5-fluorouracil treats AK, BCCs and SCCs.

These conventional skin cancer treatments are considered as the methods of choice by dermatologists and pharmaceutical companies, regardless that, with all such treatments, scarring is inevitable, and the psychological issues accompanying such "acquired disfigurement" are usually very pronounced. Consequences of these treatments include body-image issues, anxiety, post-traumatic stress disorder, depression, and a poorer quality of social and family life.

More recently a progressive topical cream formulation Curaderm, containing the anticancer solasodine glycosides, solamargine and solasonine, have reportedly shown to have advantages over conventional treatments.

Plant-derived glycoalkaloids solamargine, solasonine, mono- and di-glycosides of solasodine, known as BEC [1] induce remarkable anticancer effects in cell culture [2], animals [3], and humans [4]-[9].

Solamargine accounts for 86%, solasonine 9%, mono- and di-glycosides of solasodine 5% of neoplastic activity in BEC [10].

BEC targets receptor mutant proteins on cancer cell membranes. BEC binds to these characterised specific receptors and is subsequently internalised by cell receptor-mediated endocytosis, followed by the anticancer sequelae of identifiable anticancer pathways such as cell survival [11], tumor suppressor [12], lysosomal [13], mitochondrial [14], caspase activation [15], death receptor [16], protein kinase [17], pathways and signal pathways that impede invasion/migration and multidrug resistance [18].

BEC is effective against a wide variety of cancer cells including skin cancer with high therapeutic indices [9].

It is now well established that BEC in a topical cream formulation, Curaderm, is very effective in treating AK [9] [19], BCC [9], SCC [9] and shows promise for treating stages 0 to 2 melanoma [9] [20].

Self-administered, non-invasive topical Curaderm pharmacotherapy offers innumerable benefits, unavailable with conventional therapies. Curaderm pharmacotherapy has shown to be preferable to invasive procedures, especially in cases of multifocal lesions, unclear lesion edges, risk of hypertrophic scarring and/or keloids resulting in disfiguring scars, surgical risk factors and localisation in some areas such as the face and in elderly patients.

The common features of conventional treatments are non-specificity without targeting the tumour itself, leading to unwanted adverse effects in the surrounding tissue such as scar formation or other cosmetically disfiguring outcomes. Treatment successes and morbidity of these treatments are questionable and mostly depend on the skill of the operator of the procedure.

Although the effectiveness of Curaderm pharmacotherapy for treating skin cancer is well established, comprehensive clinical features of the lesions during treatment have not been reported. A single case study reported that during treatment with Curaderm the cancer lesion size increases, followed by a decrease in size, ultimately resulting in complete elimination of the cancer.

Here it is confirmed that in a large number of patients, there is indeed an initial increase in size of the lesions treated with Curaderm, followed by a reverse course, leading to complete removal of the skin cancer. More importantly it is now shown that by using unpublished data of a phase 3 double-blind, randomized, placebo-controlled, parallel, multicenter study that the antineoplastic agent BEC in the topical cream Curaderm is responsible for these observed changes in lesion sizes. The mode of action and the type of cell death explains the excellent cosmetic sequelae. The efficacy and toxicity sections of this phase 3 clinical trial have previously been reported [21]. The phase 3 clinical trial was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (1996). The protocol and patient informed consent were reviewed and approved by the Independent Ethics Committee for each of the 10 study centres.

2. Methods

2.1. Study Design

The study was designed as a multicenter, double blind, and randomized, vehicle-controlled clinical trial. Curaderm (also known as Zycure) was used as the active test medication and vehicle (Curaderm cream absent BEC) was used as the placebo control. BCCs of varying sizes in the study, confirmed histologically, included the following variants: nodular, cystic, pigmented, superficial and morphea-type.

2.2. Assignment to Treatment Groups

Curaderm and vehicle cream were randomly assigned to patients at a ratio 2:1, respectively. Ninety-four patients were randomized (n = 62, Curaderm, n = 32, vehicle). The investigator and patients were blinded to treatment. Curaderm and vehicle cream were visually indistinguishable.

2.3. Method of Application

The cream was applied to the lesion every 12 h under occlusive dressing for 8 weeks. Both Curaderm and the vehicle produced local irritation and erosion of the lesion. Hence, there was no bias of the patient or investigator.

2.4. Patient Inclusion Criteria

Patients aged 18 years and over, with 1) histologically confirmed BCC of any type and 2) a lesion size of at least 0.5 cm in diameter were included in the study.

2.5. Patient Exclusion Criteria

Excluded from the study were patients 1) Who were pregnant or lactating; 2) With known sensitivity or allergy to Curaderm; 3) Being immunosuppressed; 4) Who had used 5-FU or topical tretinoin within the preceding 2 months; 5) With a history of recurrent BCC after surgery, cryotherapy, or radiotherapy.

2.6. Patient Visits and Evaluation

Patients with a clinical diagnosis of BCC were screened at visit 1 by doing blood tests (haematology and biochemistry), urine dipstick and 2-mm punch biopsy for histological confirmation. A fortnight later, at visit 2, treatment was initiated for eligible patients. Thereafter, visits 3 - 6 were conducted every 2 weeks for evaluation of response to treatment as well as to note any adverse event related and unrelated to the application site. At visit 6, blood, urine, and biopsy tests were repeated to note any significant differences and confirm success or failure.

2.7. Post Treatment Follow-Up

Successfully treated patients were followed-up at 6-month intervals for a year. Failures were withdrawn and treated by alternative methods.

2.8. Efficacy

The efficacy endpoint was the complete healing of the lesion after treatment as confirmed by histological report from a 2 mm skin biopsy taken from the periphery of the site of the lesion [21].

2.9. Safety

Adverse Events—Patients were monitored for the occurrence and reporting of AEs throughout the treatment and follow-up periods [21].

Clinical laboratory tests—Haematology, biochemistry and urinalysis evaluations [21].

3. Results and Discussion

Efficacy (intention-to-treat population) at 8 weeks, as previously reported, was 66% in the Curaderm group, compared to 25% in the vehicle group ($P < 0001$; Cochran-Mantel-Haenszel test). Ninety percent of the Curaderm group completed follow-up at six-month intervals for 1 year, of whom 78% had no recurrence. There were no major treatment-related adverse effects [21].

Cosmetic evaluation—assessment of change in appearance

Assessment of change-in-appearance at visit 7 (6 months after cessation of treatment) and visit 8 (one year after cessation of treatment) for both treatment

groups indicate that there were no statistical differences in cosmetic evaluation between the Curaderm group and placebo group (p = 0.272 at 6 months and p = 0.202 at 12 months).

Changes in size of the lesions

Table 1 shows a summary of the diameters of lesions from visits 1 to visit 8 (weeks −2 to 52).

Table 1. Evaluation of lesions—diameter of lesions.

			Diameter of Lesion by Treatment Group (mm)	
			Curaderm (n = 62)	Placebo (n = 32)
Visit	Week	Summary Statistic	Lesion Size	Lesion Size
1	−2	Mean	12.5	12.9
		SD	5.24	7.93
		Minimum	5	5
		Median	11	11
		Maximum	30	50
		No. of Patients	62	32
2	0	Mean	12.1	13.2
		SD	5.13	7.78
		Minimum	5	7
		Median	10	11
		Maximum	30	50
		No. of Patients	62	32
3	2	Mean	16.9	13.8
		SD	7.82	7.85
		Minimum	5	6
		Median	15	12
		Maximum	50	50
		No. of Patients	57	32
4	4	Mean	18.2	12.9
		SD	12.24	6.48
		Minimum	1	5
		Median	16	12
		Maximum	70	40
		No. of Patients	54	32
5	6	Mean	16.2	11.5
		SD	10.19	4.63
		Minimum	2	5
		Median	15	11

Continued

		Maximum	52	25
		No. of Patients	51	32
6	8	Mean	14.1	11.2
		SD	9.93	5.82
		Minimum	0	0
		Median	14	11
		Maximum	55	25
		No. of Patients	51	31
7	26	Mean	5.4	12.9
		SD	7.02	7.66
		Minimum	0	0
		Median	4	13
		Maximum	30	22
		No. of Patients	36	8
8	52	Mean	5.6	9.2
		SD	7.2	7.82
		Minimum	0	0
		Median	4	6
		Maximum	30	2
		No. of Patients	31	5

The number of patients is not the same at each visit because of patient withdrawals or because the lesion diameter was not recorded.

Before commencement of treatment with Curaderm the sizes of the lesions were represented by a six-fold difference, during treatment with Curaderm these differences increased by a factor of seventy, which is reflected by the high standard deviations. In the case of the placebo treatment group, before commencement the ranges of the sizes of the lesions were similar to the treatment with the Curaderm group. However, these differences in sizes remained similar during and after treatment with the placebo group.

The mean lesion diameter in the Curaderm group increased from 12.1 mm at visit 2 (commencement of treatment) to 16.9 at visit 3 (2 weeks of treatment) and 18.2 mm at visit 4 (4 weeks of treatment). The mean lesion diameter then decreased at visit 5 (6 weeks of treatment) through to visit 8 (12 months after cessation of treatment) (16.2 mm at visit 5 (6 weeks of treatment); 5.6 mm at visit 8 (12 months after cessation of treatment). In the vehicle placebo group, there were little changes in lesion diameter from visit 2 to visit 6 (the mean diameter in the vehicle group was 13.2 mm at visit 2, 13.8 mm at visit 3, 12.8 mm at visit 4, 11.5 mm at visit 5, and 11.2 mm at visit 6).

Table 2 provides summary statistics for the change in diameter of the lesions from visit 2 (start of treatment) to visit 8 (12 months after cessation of treatment).

Table 2. Evaluation of lesions—change in diameter of lesion from visit 2 (start of treatment).

			Diameter of Lesion by Treatment Group (mm)		
			Curaderm (n = 62)	Placebo (n = 32)	
Visit	Week	Summary Statistic	Lesion Size	Lesion Size	
3	2	Mean	5.0	0.6	<0.001
		SD	5.54	2.97	
		Minimum	−2	−4	
		Median	4	0	
		Maximum	30	12	
		No. of Patients	57	32	
4	4	Mean	6.3	−0.3	<0.001
		SD	11.16	3.76	
		Minimum	−8	−10	
		Median	4	0	
		Maximum	60	10	
		No. of Patients	54	32	
5	6	Mean	4.2	−1.7	0.030
		SD	9.56	7.20	
		Minimum	−8	−35	
		Median	2	0	
		Maximum	36	10	
		No. of Patients	51	32	
6	8	Mean	2.4	1.9	0.239
		SD	10.67	10.03	
		Minimum	−25	−50	
		Median	0	0	
		Maximum	39	10	
		No. of Patients	51	31	
7	26	Mean	−6.9	−1.6	0.074
		SD	8.52	3.42	
		Minimum	−21	−9	
		Median	−6	−2	
		Maximum	12	3	
		No. of Patients	36	8	
8	52	Mean	−6.7	−3.0	0.312
		SD	7.84	3.54	
		Minimum	−20	−9	

Continued

Median	−5	−2
Maximum	12	0
No. of Patients	31	5

p-value from Mann-Whitney U-test. The number of patients is not the same at each visit because of patient withdrawals.

This table shows that for the placebo vehicle group there was little change in diameter over the first 8 weeks of the study with mean changes of 0.6 mm at visit 3, −0.3 mm at visit 4, −1.7 mm at visit 5, −1.9 mm at visit 6. In the Curaderm group, however, there was a mean increase of 5 mm at visit 3, 6.3 mm at visit 4, 4.2 mm at visit 5, 2.4 mm at visit 6. The differences in changes in lesion size were significant at visits 3, 4 ($p < 0.001$; and 5 ($p = 0.030$; Mann-Whitney U-test), with the Curaderm group showing a significant increase in lesion size.

Both treatment groups showed decreases in lesion size during the follow-up period (visits 7 and 8). There was a mean change in diameter of −6.9 mm at visit 7 and −6.7 at visit 8 for the Curaderm group, and −1.6 mm at visit 7, and −3.0 mm for the vehicle group. There was no evidence of a significant difference between the treatment groups at visits 7 and 8. There was no statistical difference in lesion size with the placebo group throughout the study.

The efficacy conclusions of this study that Curaderm is more effective in the treatment of BCC compared to a vehicle cream when applied to the lesions twice daily for 8 weeks has previously been reported [21]. Curaderm is a safe therapy for BCC with a cure rate of 66% at 8 weeks and 78% at 1-year follow-up. Subsequent studies with Curaderm when treating BCC for over 8 weeks yield higher cure rates, when treatment period is extended for 14 weeks, over 90% cure rate is obtained with no recurrences for over 5 years [9]. The keratolytic effects of salicylic acid and urea in the placebo formulation resulted in 25% efficacy in the placebo group.

A previous study with one patient reported that during treatment of skin cancer with Curaderm, the lesion first became bigger as cancer cells beneath the surface and laterally located, died followed by reduction of the size of the lesion with subsequent healing [9] [22].

Figure 1 shows that indeed this phenomenon occurs when various types and sizes of BCCs are treated with Curaderm. The large variation in the sizes of the lesion showing initial increase in size followed by lesion-size reduction and subsequent healing attest to an occurrence that is consistent with the treatment of BCC with Curaderm.

These observations are the consequences of the mode of action of BEC, the active anticancer solasodine glycosides ingredient, in Curaderm. The key properties of BEC, and thus Curaderm, are 1) specificity, BEC only interacts with cancer cells and not normal cells; 2) BEC is internalised by cell receptor-mediated endocytosis; 3) BEC kills cancer, but not normal cells by various biological pathways; 4) BEC kills the cancer cells by apoptosis and not necrosis.

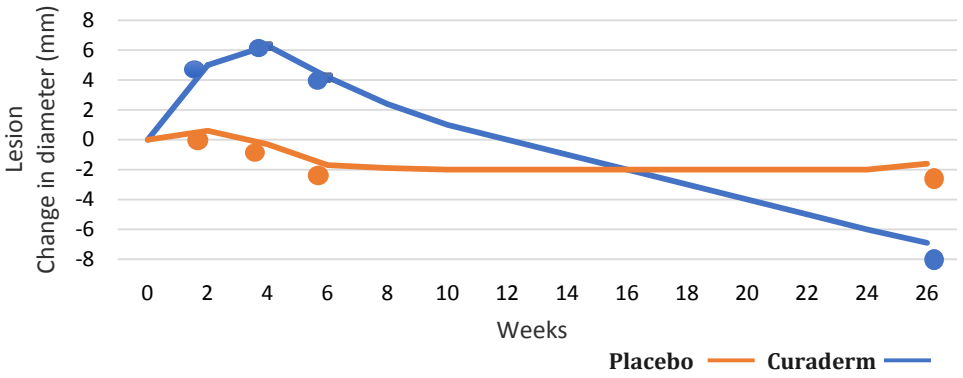


Figure 1. The effect of treatment time on the change in lesion diameter.

During treatment of skin cancer with Curaderm, initially, because of the abundance of cancer cells, including deep seated and lateral skin cancer cells, the treated lesion becomes larger, and the lesion ulcerates, at this stage and throughout the treatment, non cancer skin cells are unaffected and continue to multiply. In particular, up to 4 weeks of treatment with Curaderm, the ratio of killed cancer cells-to-multiplying normal cells is in favor of killed cells giving the appearance of the lesion increasing in size. As treatment time progresses this ratio of cancer cell death-to-new normal cell growth decreases, ultimately reaching the stage whereby no more cancer cells are present.

It is important to note that regeneration of new epidermis at the application site within the first 4 - 5 weeks of treatment with Curaderm occurs, despite continued application of Curaderm, and cancer cells dying. Histological examination shows acanthosis of the regenerated epidermis on 8-week post treatment biopsy [21].

These observations were absent with the placebo arm of the study. These investigations show clearly that BEC in Curaderm acts preferentially in the elimination of transformed cells as opposed to normal cells and are in agreement with cell culture, animal, and human studies [9].

The extent of the changes in size of the lesions and the duration of these changes during treatment depend on the original pre-treatment size and characteristics of the skin cancer.

Figure 2 illustrates that Curaderm selectively and specifically seeks out and eliminates skin cancer cells from normal skin cells, which remain unaffected. Whilst the skin cancer cells are dying by the Curaderm therapy, the normal cells are alive, multiplying and replacing the dead cancer cells during treatment!

Curaderm therapy results in apoptosis of the cancer cells, the white blood cells (phagocytes) mop up the remains of the dead cancer cells [21]. This results in the replacement of the killed cancer cells with healthy normal skin cells during treatment. Consequently excellent cosmetic outcomes occur with little or no scarring.

The reported cosmetic outcome of Curaderm therapy with skin cancer [9] is explained by the mode of action of Curaderm in killing cancer cells by apoptosis [21].

This is contrasted to the mode of actions of conventional skin cancer treatments, including surgery, Mohs micrographic surgery, curettage and electrodesiccation, chemotherapy, radiation, cryotherapy or laser therapy whereby necrosis occurs leading to scar formation. Using these conventional skin cancer treatments some patients may scar more than others depending on their tendency towards keloid scarring, their skin type and the conventional procedure used.

Figure 3 and Figure 4 show histological analyses of skin cancer lesions after conventional and Curaderm treatments.

Figure 5 illustrates a clinical observed scar five years post surgical treatment of a basal cell carcinoma. Figure 6 shows that there is no scar present five years post treatment of a basal cell carcinoma with Curaderm.

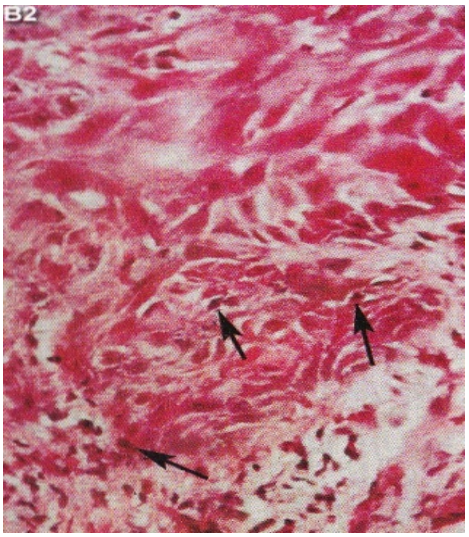


Figure 2. Histological diagnosis of a skin cancer during Curaderm therapy. Arrows indicate cancer cells being killed during Curaderm treatment. The observation of this type of cell death by apoptosis caused by Curaderm is similar to those obtained in cell culture studies. Normal skin cells are unaffected and replace the dead cancer cells.

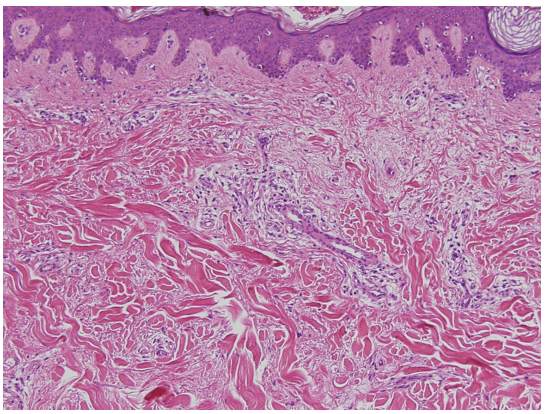


Figure 3. Histological diagnosis showing an established scar obtained by traditional treatments of skin cancer with horizontally oriented thicker and more densely packed hyalinised collagen bundles and loss of all skin appendages.

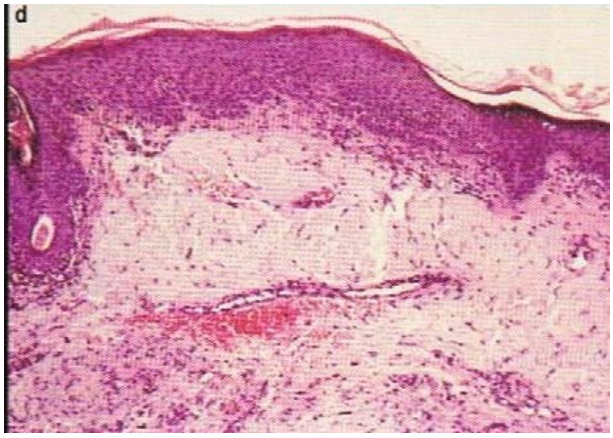


Figure 4. Histological diagnosis showing a biopsy after treatment of a basal cell carcinoma with Curaderm. Fine collagen and elastic fibres, present in normal skin, are seen.

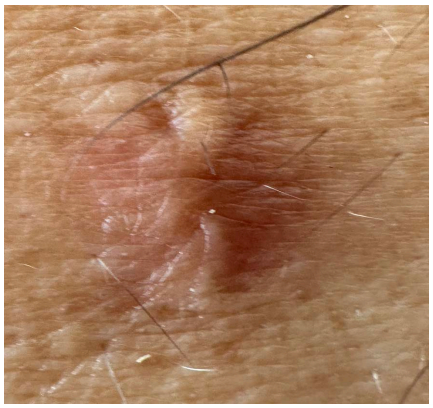


Figure 5. Clinical observed scar five years post surgical treatment.

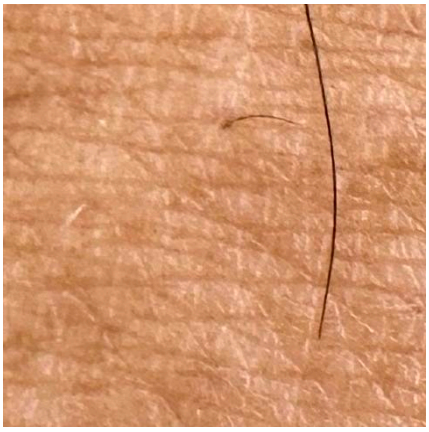
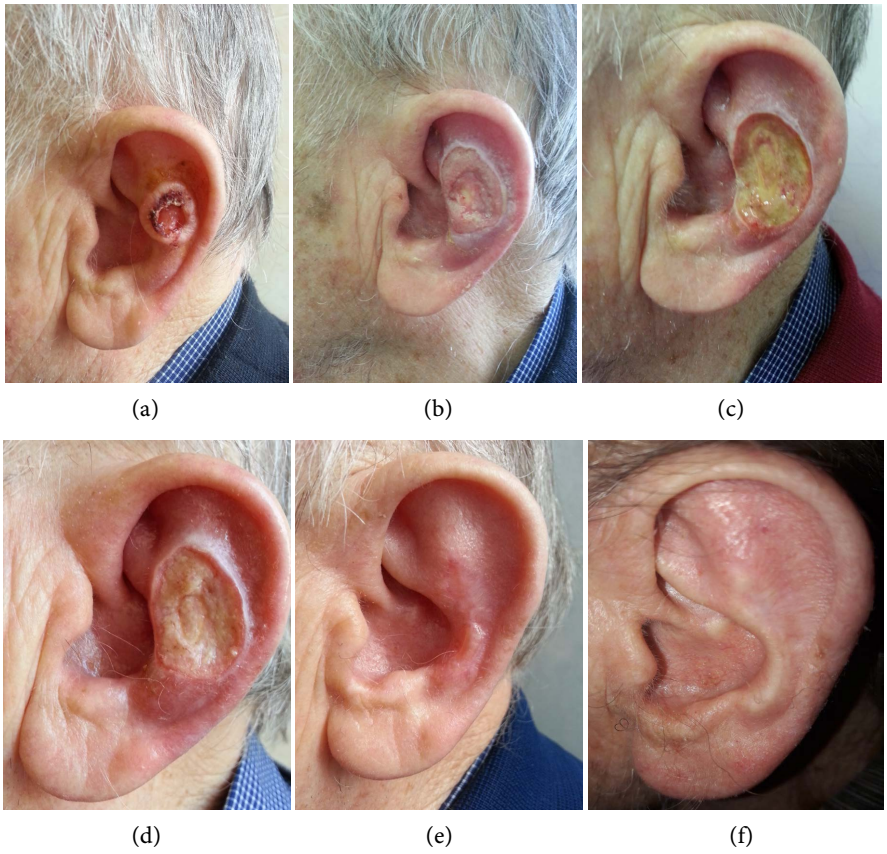


Figure 6. No scar present.

This is consequential to the mode of action of Curaderm by apoptosis (**Figure 2**) which is reflected by the impressive observed cosmetic outcomes with Curaderm therapy (**Figures 7(a)-(f)**) [9] [22] [23]. The photos in **Figure 7** also show clearly that during initial treatment of Curaderm with skin cancer, the treated lesion becomes larger then reverse course until complete elimination.



(a) (b) (c)

(d) (e) (f)

Figure 7. Patient, 85 years. BCC on left ear, before Curaderm pharmacotherapy (a), after 17 days treatment (b), after 28 days treatment (c), after 60 days treatment (d), after 74 days treatment (e). No relapse after 5 years treatment (f).

4. Conclusions

Topical Curaderm pharmacotherapy is effective in treating skin cancers. Placebo controlled studies show that the observed minor side effects are caused by the excipients in the formulation. Over 90% complete regression of skin cancers treated with Curaderm is obtainable, recurrences are very low, and the cosmetic outcomes are impressive.

It is important that both the health-care professional and the patient are aware that when treating skin cancer with Curaderm, initially (for the first 4 weeks of commencement of treatment), the lesion will appear to become larger. This is part of the treatment regimen and should not be perceived as the lesion becoming worse, but rather this should be expected. Because of the specificity and mode of action of BEC (the anti cancer ingredient in Curaderm), apoptosis (self suicide) in cancer cells but not normal skin cells occurs. This results in cosmetic outcomes far beyond those obtained with conventional skin cancer treatments. Further studies with Curaderm on melanoma, stages 0 - 2, are ongoing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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