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Treatment of Skin Cancer with a Selective Apoptotic-Inducing Curaderm^{BEC5} Topical Cream Containing Solasodine Rhamnosides

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Abstract

Solasodine rhamnosides produced in plants as secondary metabolites, are safe and effective when treating a variety of cancers, including non-melanoma skin cancers. They are cytotoxic against multi-drug resistant tumor cells, stimulate lasting immunity against cancer, are not mutagenic and display anti-mutagenic properties. These antineoplastics, through cellular specific receptor-mediated actions, directly induce apoptosis by triggering extrinsic and intrinsic apoptotic pathways in cancer cells but not normal cells. Curaderm^{BEC5} contains solasodine rhamnosides and is a topical formulation for the treatment of keratoses and non-melanoma skin cancers. The mode of action, together with the selectivity towards cancer cells, with Curaderm^{BEC5} therapy, results in outstanding beneficial outcomes. This study shows graphically and pictorially that Curaderm^{BEC5} seeks and destroys basal cell carcinoma whilst normal skin cells replace the dead cancer cells during therapy, emanating into impressive cosmetic end results. The clinical observations with Curaderm^{BEC5} therapy reveal that initially the lesion size increases over four-fold due to the interaction of Curaderm^{BEC5} with deeper and more lateral tumor cells, followed by a decrease in size, ultimately, resulting in complete elimination of the basal cell carcinoma.

Keywords

Skin Cancer, BEC, Solamargine, Curaderm, Apoptosis, Solasodine Rhamnosides

1. Introduction

Skin cancer is the most common form of human cancer. Over the past three decades, more people have had skin cancer than all other cancers combined [1]. Each year there are more new cases of skin cancer than the combined

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incidence of cancers of the breast, prostate, lung and colon [2].

Actinic keratosis is the most common cutaneous precancer; it affects more than 58 million Americans [3]. Approximately 36% of all basal cell carcinomas (BCCs) and 65% of all squamous cell carcinomas (SCCs) arise in lesions that previously were diagnosed as actinic keratoses [4].

In the USA alone, more than 2.2 million people develop over 3.5 million non-melanoma skin cancers every year [2]. One in five Americans will develop skin cancer in the course of a lifetime [5]. Between 40 and 50 percent, that is approximately 1 in 2, of Americans who live to 65 years will have either a BCC or SCC at least once [6].

BCC is the most common form of skin cancer; an estimated 2.8 million BCCs are diagnosed annually in the USA. BCCs are rarely fatal, but can be highly disfiguring if allowed to grow. Over three thousand deaths from advanced BCCs occur annually in the USA [7].

SCC is the second most common form of skin cancer. An estimated 700,000 cases of SCC are diagnosed each year in the USA. Between 3900 and 8800 people died from the disease in the USA in 2012 [8]. Organ transplant patients are up to 250 times more likely than the general public to develop SCC [9]. The incidences of BCCs and SCCs have been rising at alarming rates [8] [10].

A variety of treatments such as surgical excision, curettage and electrocautery, cryotherapy, Mohs micrographic surgery, chemotherapy, photodynamic therapy, radiotherapy and imiquimod cream are available for non-melanoma skin cancers with good outcomes, especially if the cancers are detected and treated in the early stages of development. However, many limitations and disadvantages of these most widely used treatments have previously been described [11] [12].

The annual cost of treating non-melanoma skin cancers in the USA is estimated at $4.8 billion [13]. The average annual cost for skin cancer increases remarkably each year. For example, in the USA between the period 2002-2006 and the period 2007-2011, the average annual cost for skin cancer treatment increased by more than 126%, compared to 25.1% for all other cancers [13].

It is not surprising that the quests for innovative skin cancer treatments are on-going.

A mixture of naturally occurring glycoalkaloids, known as BEC, has been shown to be potent anticancer agents. BEC is found in plants of the nightshade family like aubergine [14] and is composed of solamargine (33%), solasonine (33%) and di-and monoglycosides of solasodine (33%) [15]. These solasodine rhamnosides are produced in plants as secondary metabolites and cause cancer cells to commit suicide (apoptosis) [16]-[21], are cytotoxic against multi-drug resistant tumor cells [20], stimulate lasting immunity against cancer [18] are not mutagenic and even display anti-mutagenic properties [17].

A cream containing BEC, known as Curaderm^{BEC5}, is effective and safe in treating human skin cancers [11] [12] [14]-[17]. Many studies have reported that Curaderm^{BEC5} treats a wide variety of skin cancers in terms of types, sizes, location including sensitive areas such as the periocular [12] and cancer on the penis [22] [23]. However, there is no published study that illustratively shows graphically and pictorially, how Curaderm^{BEC5} specifically seeks and destroys skin cancer and simultaneously allows normal skin cells to regrow and replace the dead cancer cells. These main features distinguish the superior clinical and cosmetic results obtained with Curaderm^{BEC5} therapy compared with other treatment procedures.

This is the first report that exemplifies graphically and pictorially, the sequential uniqueness of Curaderm^{BEC5} therapy.

2. Patient

A 64-year-old female chemical engineer had previously been treated for four BCCs. The first one was surgically removed in 2009, the second was frozen off in 2010, the third and fourth were removed by surgery in 2012 and 2013 respectively.

A fifth BCC lesion was present for about 3 years. Her doctor, who diagnosed her lesion, insisted on surgery for the fifth lesion but the patient did not want surgery again, and elected to be treated with Curaderm^{BEC5} therapy. The patient exhibited a circular BCC lesion of 15 mm in diameter, on the chest near the left arm.

3. Materials and Methods

The topical cream formulation Curaderm^{BEC5} is available to patients in several countries. Curaderm^{BEC5} contains BEC at 0.005% in a cream formulation [11] [12] [14] [17] [22]-[24]. The cream was applied three times daily

(when possible every 8 hours) at a dose of 0.1 g cream under occlusive dressing (micropore paper tape) until the lesion had clinically regressed. Measurements and photographs were taken throughout the treatment. Because the lesion was close to being circular, and the changes in sizes during treatment retained the circular shapes, the diameters of the lesions were measured and were used to calculate the area of the lesions in mm^2. The calculated areas represent approximate two-dimensional figures and do not represent the three-dimensional volumes of the lesions. The sizes of the lesion before, during and after Curaderm^{BEC5} therapy were measured in situ on the skin's surface and not from the photographs. The photographs did not all have identical magnifications and are unadulterated.

4. Results

Figure 1 shows the BCC after application of Curaderm^{BEC5} and covered with micropore paper tape. Before treatment commenced, the diameter of the BCC was 15 mm.

Figure 2 shows the changes in areas of the BCC lesion relative to pre-treatment area vs. treatment and beyond treatment times. The lesion responded rapidly to the treatment. There was an immediate increase in lesion size after commencement of Curaderm^{BEC5} therapy. The size of the lesion increased more than four-fold and peaked at approximate 30 days of treatment. On-going treatment with Curaderm^{BEC5} then resulted in a decline of lesion size, at day 59 the size had returned to the original pre-treatment size. Continuing treatment caused the lesion to further reduce in size and after 86 days of treatment the lesion was completely eliminated. From approximately

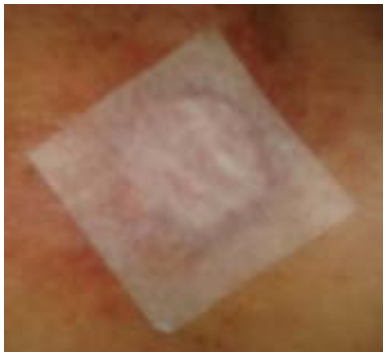

Figure 1. BCC after application of Curaderm^{BEC5} and covered with micropore paper tape. The diameter of the lesion before treatment was 15 mm.

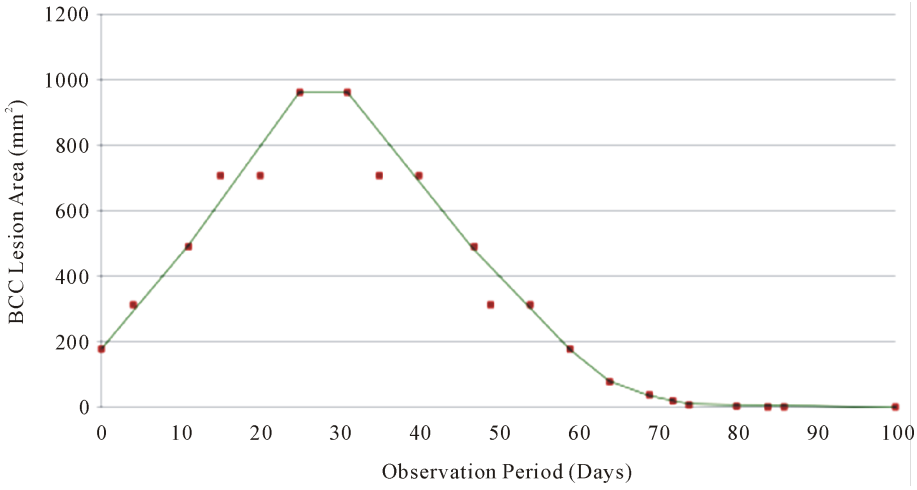

Figure 2. Curaderm^{BEC5} therapy caused an immediate change in BCC lesion size and after 30 days treatment, peaked at over a 4-fold increase in size. Continuous treatment after 30 days resulted in a decrease in lesion size and complete removal of the BCC was attained after 86 days of Curaderm^{BEC5} therapy.

day 30 treatment, regeneration of new epidermis at the application site occurred until the end of therapy (day 86) despite continued three times daily application of Curaderm^{BEC5}.

Figure 3 illustrates the appearances of the lesion during various stages of Curaderm^{BEC5} therapy. No photograph of the pre-treatment lesion is available. However, the pre-treatment lesion was similar in appearance as day 4 treatment but only smaller in size. The photographs epitomize the initial increase in size of the BCC lesion followed by a reduction in size until the lesion was completely removed during Curaderm^{BEC5} therapy.

During Curaderm^{BEC5} therapy the cancer cells were being eliminated whilst new non-cancerous cells were replacing the dead cancer cells. This is clearly shown from day 30 treatment to the end of Curaderm^{BEC5} therapy at day 86. Clinically there was no scar tissue at the completion of the treatment.

This patient experienced mild itching and stinging surrounding the treated lesion for the first week of Curaderm^{BEC5} therapy.

5. Discussion

The incidences of non-melanoma skin cancers are rising at disturbing rates and the annual cost for skin cancer treatment increased five-fold more when compared with all other cancers [13]. The treatment for these non-melanoma skin cancers depends on their type, size and location, the number to be treated, and the preference or

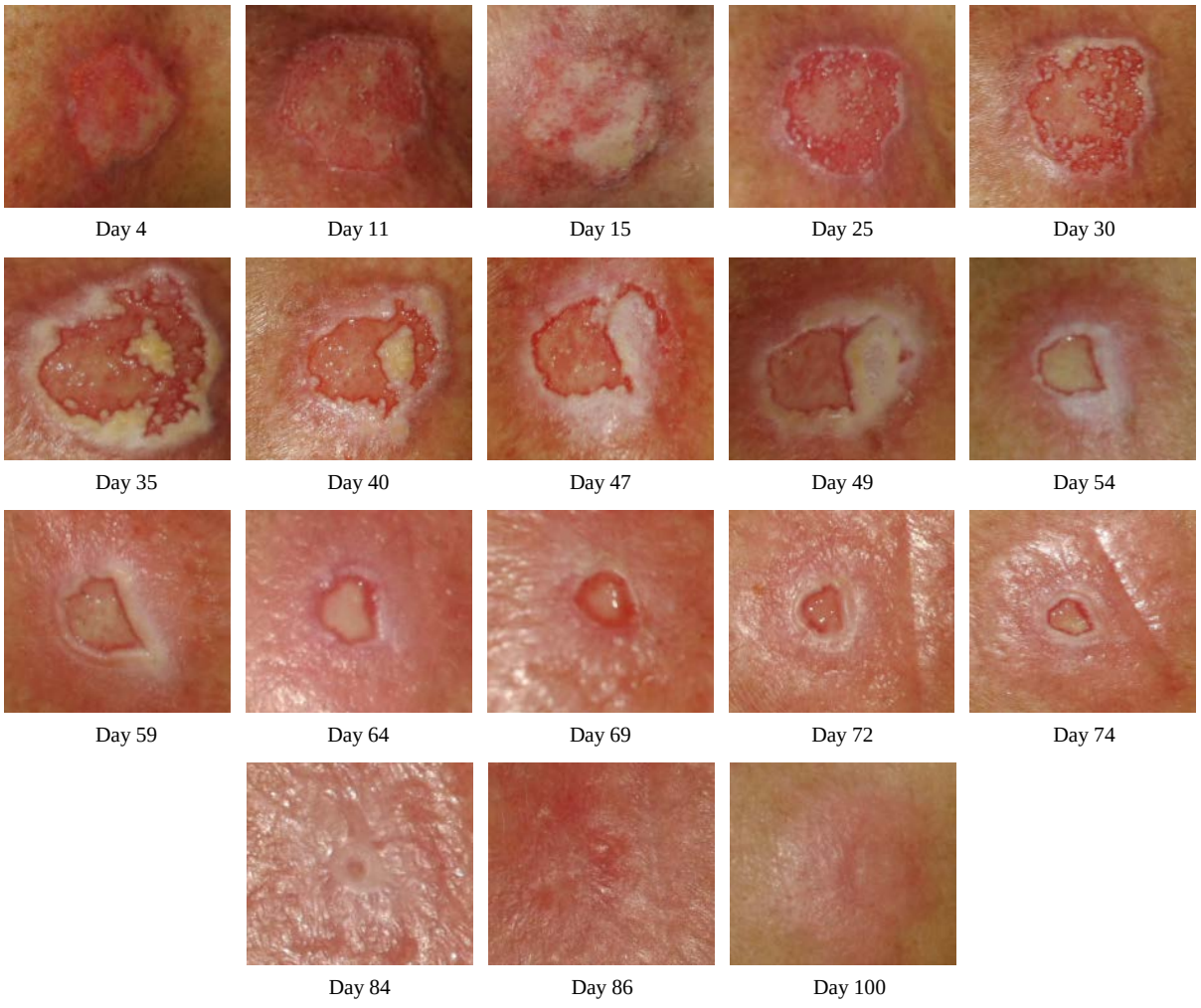

Figure 3. Appearances of BCC lesion during and after Curaderm^{BEC5} therapy. Curaderm^{BEC5} was applied 3 times daily at a dose of 0.1 g cream and covered with micropore paper tape occlusive dressing. The indicated days refer to the treatment periods. Cancer cells were being eliminated and replaced with normal epidermal skin cells during treatment. Treatment was stopped only after the original BCC lesion had healed (day 86).

expertise of the doctor. A variety of treatments have contributed significantly to human health, especially when treating early-detected non-melanoma skin cancers.

However, there are also many limitations and disadvantages using these techniques, such as, requirement of local anaesthetics, procedural complications, disfigurement, long treatment periods, changes in pigmentation, high recurrence rates and possible requirements of surgical reconstruction after treatment [23] [24]. Therefore, the search for innovative safe and effective treatments for skin cancers is a high priority.

One such discovery has been obtained using natural BEC solasodine rhamnosides.

The antineoplastic mode of action of solasodine rhamnosides, solamargine and solasonine, present in Curaderm^{BEC5}, may explain the remarkable observed clinical outcomes. Specific endogenous endocytic lectins (EELs) have been identified on cancer cells [16]. The EELs have been further characterized as rhamnose binding protein (RBP) receptors [21] [25]. RBP receptors are present on cancer cells but not normal cells [16] [21] [25]. RBP receptors bind the solasodine rhamnosides (BEC). BEC is then internalized into the cancer cell by receptor-mediated endocytosis. BEC then interacts with the lysosomes and mitochondria resulting in the triggering of extrinsic and intrinsic apoptotic pathways in the cancer cells by up-regulating the expression of external death receptors, such as tumor necrosis factor receptor 1 (TNFR-1), Fas receptor, TNFR-1 associated death domain and Fas-associated death domain [26] [27]. BEC enhances the intrinsic ratio of Bax to Bcl-2 by up-regulating Bax and down-regulating Bcl-2 and Bcl-x expressions. These effects result in activation of Caspase-8, -9 and -3 in cancer cells [23] [26]-[32] indicating that BEC triggers extrinsic and intrinsic apoptotic pathways in cancer cells and causes apoptosis (programmed cell death) to cancer cells. Curaderm^{BEC5} causes cancer cells to commit suicide.

These events may explain the clinical observations that treatment with Curaderm^{BEC5} results in elimination of cancer cells only and not normal cells. Very importantly, as shown in this communication, whilst Curaderm^{BEC5} is destroying cancer cells, normal cells are replenishing the dead cancer cells and this exceptional occurrence translates to the observed cosmetic effects of Curaderm^{BEC5} therapy. Moreover, Curaderm^{BEC5} therapy clears cancer cells whether they are proliferating or not [23].

Adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to the rates observed in clinical practice. However, a small but significant number of patients in the clinical trials as well as in clinical practice have experienced burning sensations that have lasted for several minutes after application of Curaderm^{BEC5}. Other skin reactions are erythema, pruritis, swelling, postulation and ulceration [33]. Curaderm^{BEC5} has no adverse effects on the liver, kidneys or hematopoietic system [33].

The clinical events with Curaderm^{BEC5} reveal that initially the lesion size increases significantly due to interaction of Curaderm^{BEC5} with deeper seated and more lateral tumor cells. As treatment progresses, the size of the lesion decreases due to the elimination of Curaderm^{BEC5} affected cancer cells, which are replaced with normal skin cells. Treatment is continued until the lesion is totally cleared. These observations indicate that Curaderm^{BEC5} is preferential in its application to transformed cells [24]. Curaderm^{BEC5} therapy is vastly different than all other skin cancer therapies, but may be considered comparable to the microscopic observations when Moh's treatment is being performed from whence continual surgical removals of the tumor cells are done, until complete excision is achieved. However, with Curaderm^{BEC5} therapy, no surgery is required, only application of the cream is necessary. After Curaderm^{BEC5} therapy, no reconstructive surgery is required, the cosmetic result is impressive and, as shown previously, functionality of the cancer treated tissue is preserved [22] [23].

Many other studies have shown that the recurrence rates of Curaderm^{BEC5} treated skin cancers are very low. Patients who have been followed-up for over 5 years confirmed the very low recurrence rates [11] [12] [23] [24] [34]-[37]. A limitation of Curaderm^{BEC5} therapy is the length of treatment period, but this is far outweighed by the outstanding end result.

The duration of Curaderm^{BEC5} therapy appears to vary depending on size of the particular lesion rather than type [33].

In the initial stages of Curaderm^{BEC5} therapy, which may vary from one day to several weeks depending on size and type of cancer, the treated lesion will become larger. The reaction of the tumor treated with Curaderm^{BEC5} may be unsightly at the initial stages during treatment. The reason for the initial increase in lesion size is that Curaderm^{BEC5} is seeking and destroying the cancer cells that are originally not visible to the bare eyes.

At this stage some patients may be discouraged to continue treatment because the cancer seems to be getting worse and not better. In addition, some patients may experience pain or a burning sensation for some time after Curaderm^{BEC5} is applied to the lesion. These possible observations are all part of the treatment regime. The pos-

sible pain experienced, is due to the salicylic and urea contents and not the active ingredient BEC. Salicylic acid and urea help with the penetration of BEC to kill the deep-seated cancer cells.

After some time during the treatment, the lesion will start to reduce in size. At this stage most of the cancer cells are eliminated by the treatment. Treatment should continue and because the lesion is becoming smaller, less Curaderm^{BEC5} cream is applied to the lesion.

Treatment should continue until the lesion is completely gone and replaced with normal skin. If treatment is stopped too early, some residual cancer cells may remain and over time will become a lesion again. Studies have shown if the procedure is followed diligently, all cancer cells are removed and the lesion will be cured with no recurrences for over 5 and 10 years.

No controlled clinical trials comparing the efficacy of Curaderm^{BEC5} with other treatment modalities have been reported. Nevertheless, case studies have shown that Curaderm^{BEC5} therapy was successful in eliminating skin cancers that were unsuccessfully treated by surgery, radiation therapy, photodynamic therapy, laser therapy and imiquimod therapy [33].

Another important issue to consider is the cost of treatment. In the United States alone, treatment of skin cancer amounts to US$1.8 billion each year [38] and indeed the most widely used treatments for skin cancer are costly. Any effective modality that can reduce such a financial burden to the Health Care System and to patients should be considered seriously. The cost of Curaderm^{BEC5} for treating the patient in this communication is only a fraction of other therapies [39].

An alternative, safe, efficacious, cosmetically superior and cost effective method of treatment for skin cancer which does not require physician or hospital attendance should be welcomed.

6. Conclusions

There is now a much-needed alternative available for the treatment of skin cancer. Dermatologists, plastic surgeons and radiotherapists usually jointly manage the case presented here. The fact that this patient refused to, once again, be treated with surgery reflects the sentiments and reality of the dilemma faced by those suffering with such afflictions.

A safe treatment that selectively deals with skin cancer without disturbing the healing process is exceptional. The consequential end result of such a treatment is the superior cosmetic outcome when compared to other widely used procedures. It is also beneficial that Curaderm^{BEC5} does not require continuous physician or hospital attendance.

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