Solasodine glycoalkaloids: a novel topical therapy for basal cell carcinoma. A double-blind, randomized, placebo-controlled, parallel group, multicenter study

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Abstract

Objective To assess the safety and efficacy of a 0.005% mixture of solasodine glycosides (Zycure) in the treatment of basal cell carcinoma.

Design Double-blind, randomized, and vehicle-controlled, parallel group study.

Setting Ten centers in the United Kingdom.

Participants Male, $n = 50$; female, $n = 44$; age range, 32–95 years (Table 1).

Intervention Ninety-four patients were randomized on a 2 : 1 ratio ($n = 62$, Zycure; $n = 32$, vehicle). Histologically confirmed lesions were treated double blinded, twice daily under occlusion with Zycure or vehicle for 8 weeks. Patients were reviewed fortnightly for adverse effects and overall response. Successfully treated patients were followed up at six-month intervals for a year.

Main outcome measures The primary efficacy endpoint was histologically confirmed clearance of the basal cell carcinoma (2-mm punch biopsy) at the end of 8-week treatment.

Results Efficacy (intention-to-treat population) at 8 weeks was 66% (41/62) in the Zycure group, compared to 25% (8/32) in the vehicle group ($P < 0.001$; Cochran–Mantel–Haenszel test). Ninety percent (37/41) of the Zycure group completed follow-up at six-month intervals for 1 year, of whom 78% (29/37) had no recurrence. There were no major treatment-related adverse effects, although 10 patients in Zycure group did not complete the treatment protocol for various reasons.

Conclusion We conclude that the solasodine glycoside cream Zycure is a safe therapy for basal cell carcinoma, with a cure rate of 66% at 8 weeks and 78% at 1 year follow-up.

Introduction

Nonmelanoma skin cancer is the most common malignancy worldwide among Caucasians, and accounts for over 90% of all skin cancers.[1] Eighty percent of nonmelanocytic skin cancers are basal cell carcinomas (BCC), with an estimated 2 million new cases reported by the World Health Organization annually. In the United Kingdom, there has been a 50% increase in the number of diagnoses of skin cancer in the past decade.[2] Furthermore, a patient with a primary BCC has a 40% increased risk of further diagnosis of primary BCC.

Treatments include surgery, curettage and cautery, cryotherapy, and radiotherapy depending on the site, size, and morphology of the tumors.[3] Topical therapy has been suggested for multiple superficial tumors at low-risk sites (limbs and trunk). The topical treatment 5% fluorouracil cream (5FU) has been used to treat superficial BCC.[4]

A mixture of naturally occurring glycoalkaloids has been shown to be highly effective in treating human skin cancers. This mixture consists of solasodine glycosides (Fig. 1). These compounds are found in plants of the nightshade family like aubergine.[5]

A cream containing solasodine glycosides has been formulated and tested in Australia (licensed in 1991 and marketed as "Curaderm") for solar keratosis. In an open controlled clinical trial of 28 patients with 62 lesions, complete regression was observed in 20 of 24 BCCs, 5 of 6 squamous cell carcinomas (SCC), and all 23 cases of solar keratoses. There were no systemic adverse effects and no recurrence in patients followed for 5 years.[6]

These observations motivated a subsequent open study in Australia of 72 patients, including cases of actinic keratoses (56 cases), BCC (39 cases), and SCC (29 cases) of skin, using treatment with a lower concentration (0.005%) of solasodine glycosides in a different cream formulation. This open study demonstrated regression of all treated lesions within 1–3

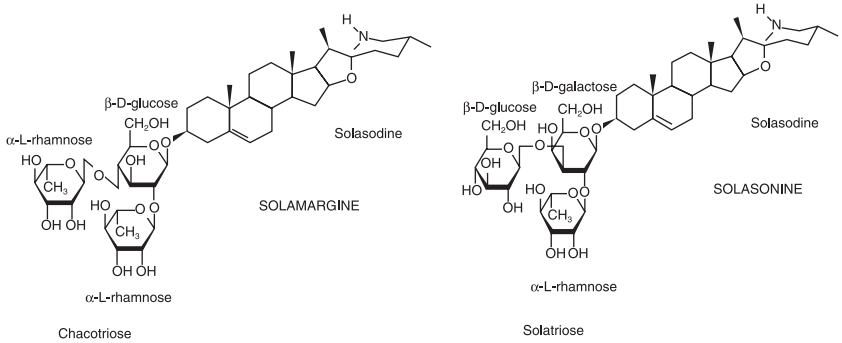

Figure 1 Molecular structure of solamargine and solasonine

weeks of treatment, confirming efficacy.[7] However, a review of the literature revealed that no data from an International Conference on Harmenisation–compliant, randomized, controlled study of glycoalkaloids exist.

We investigated the efficacy and safety of Zycure cream, containing 0.005% of solasodine glycosides (mainly solasonine and solamargine) in the treatment of BCCs.

Methods

Study design

Our study was designed as a multicenter, double-blind, randomized, vehicle-controlled clinical trial. Zycure was used as the active test medication and vehicle (Zycure cream absent the solasodine glycosides) was used as the placebol control. Approval was obtained from the Medical Ethics Committee of each study center and signed informed consent was obtained from all patients. The study was monitored independently by a research organization. BCCs included in the study, as confirmed histologically, included the following variants: nodular, cystic, pigmented, and superficial.

Assignment to treatment groups

The active medication and vehicle cream were randomly assigned in advance at a ratio of 2 : 1, respectively. The investigator, pharmacist, and the patients were blinded to treatment. Food coloring was added to the vehicle cream; hence, the active and vehicle treatments were indistinguishable.

Method of application

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

Study medication and evaluation

The vehicle is composed of the following: 15% emulsifying wax, 10% white soft paraffin, 10% salicylic acid, 5% urea, and 5% propylene glycol; Zycure, on the other hand, is composed of the vehicle + 0.005% solasodine glycosides.

Table 1 Demographics

	Treatment group	
Characteristic	**Zycure *n* = 62**	**Vehicle *n* = 32**
Age (in years): mean	68.9	70.0
Sex: male	33	17
Sex: female	29	15
Race: Caucasian	62	32

Patient inclusion criteria

Patients aged 18 years and over with (i) histologically confirmed BCC of any type except the morphoeic form, and (ii) a lesion size of at least 0.5 cm in diameter were included in this study.

Patient exclusion criteria

Excluded from the study were patients (i) who were pregnant or lactating; (ii) with known sensitivity or allergy to the active medication; (iii) being immunosuppressed; (iv) who had used 5FU or topical tretinoin within the preceding 2 months; and (v) with a history of recurrent BCC after surgery, cryotherapy, or radiotherapy.

Patients with a clinical diagnosis of BCC were screened at visit 1 by doing blood tests (hematology 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 note any adverse event related and unrelated to application site including serious adverse events (SAE; hospitalization/death). At visit 6, blood, urine, and biopsy tests were repeated to note any significant differences and confirm success (Table 2).

Post-treatment follow-up

It was decided to follow up successfully treated patients at 6-month intervals for a year. Failures were withdrawn and treated by alternative methods.

Table 2 Treatment regime

Visit	Demographic data	Punch biopsy	Blood tests	Urine test	Local irritation	Evaluation of response to treatment	Adverse events including serious adverse events
1	√	√	√	√	X	X	X
2	X	X	X	X	√	X	X
3	X	X	X	X	√	√	√
4	X	X	X	X	√	√	√
5	X	X	X	X	√	√	√
6	X	√	√	√	√	√	√

Table 3 Intention-to-treat population primary statistics

	Zycure ratio (%)	Vehicle ratio (%)
Population	62 (100.0)	32 (100.0)
Completed treatment (Visits 1–6)	52/62 (83.9)	32/32 (100.0)
Treatment success (31 + 10 withdrawals) $P < 0.001$ CMH test	41/62 (66.1)	8/32 (25.0)
Treatment failure	21/62 (33.9)	24/32 (75.0)
Number with follow-up	37/41 (90.2)	8/8 (100.0)
Recurrence at 6 months (Visit 7)	5/37 (13.5)	3/8 (37.5)
Recurrence at 12 months (Visit 8)	3/32 (9.4)	1/5 (20.0)
Overall recurrence	8/37 (21.6)	4/8 (50.0)
Success at 1 year	29/37 (78.4)	4/8 (50.0)

CMH, Cochran–Mantel–Haenszel.

Statistical analysis

The sample size was calculated assuming that vehicle cream alone could produce success in 10% and the active cream in 70%. A total of 108 patients (72 in the active group and 36 in the vehicle group) were planned to be recruited, to ensure that 72 evaluable patients would be treated for 8 weeks.

The primary efficacy endpoint was complete healing of test lesion as confirmed by a 2-mm punch biopsy upon completion of 8-week treatment. The secondary efficacy endpoints were physician's global evaluation of response to treatment, assessment of local irritation, and cosmetic outcome as evaluated by an assessment of scarring during the follow-up (categorized as none, mild, moderate, severe). The safety endpoint was assessment of the frequency, nature, and severity of adverse events and evaluation of laboratory tests done at screening and end of treatment.

The intention-to-treat (ITT) population was used to assess the primary and secondary efficacy endpoints. The ITT population included all patients who received study medication. The primary and secondary efficacy variables were analyzed by the Cochran–Mantel–Haenszel test (CMH test), adjusting for center. Summary statistics were presented by visit for each treatment group and for each laboratory parameter. For participants who withdrew and missing data, we carried forward the last observation. However, safety data were collected from all patients regardless of their completion status.

The results of this study show statistically significant differences in efficacy of Zycure and vehicle groups ($P < 0.001$) (Table 3) (66% at 8 weeks and 78% at 1 year for Zycure as compared to 25% at 8 weeks for vehicle). The 25% success rate for the vehicle group may be explained by the presence of keratolytic agents like salicylic acid and urea in the composition resulting in clearance of some tumors but, not surprisingly, result in higher recurrence rates on follow-up after 1 year. Moreover, additional analyses showed lower recurrences in the Zycure group than vehicle group (Table 3).

There were no SAEs that were considered to be likely or related to the solasodine glycosides. Notably, there were no significant differences between the two treatment groups with respect to SAEs, with six patients reporting a total of nine SAEs (Table 4).

Adverse events were listed and summarized by treatment group with a confidence interval of 95% (Table 5).

A review of laboratory data that included a full blood count, biochemistry, and urinalysis at screening and end of treatment did not reveal any clinically significant patterns of change for any parameter in the Zycure or vehicle groups.

Histopathological assessment of the ITT population revealed that approximately one-fifth manifested morphological features of apoptosis during treatment. Moreover, about half of these showed

Table 4 Patients with serious adverse events (SAE)

Treatment group	SAE	Relationship to study medicine
Zycure (treatment phase)	1. Lobar pneumonia, sepsis, death	Unlikely
	2. Metastatic neoplasm	Unrelated
Zycure (follow-up)	3. Myocardial infarction	Unrelated
	4. Myocardial infarction, death	Unrelated
Vehicle (follow-up)	1. Anemia	Unlikely
	2. Jaundice and death	Unrelated

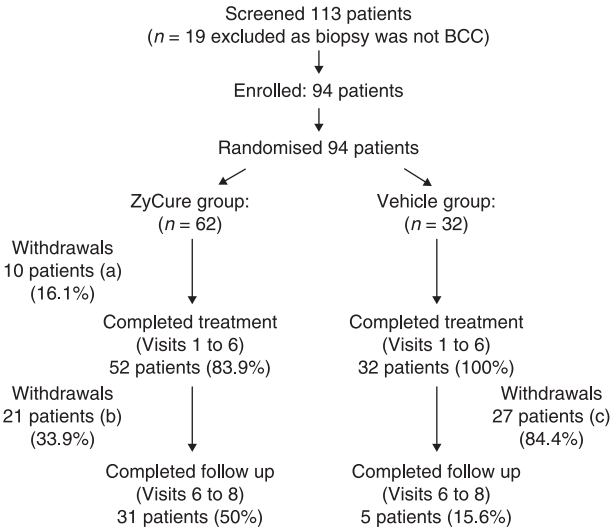

Figure 2 Results flow of participants. Notes: (i) six of the ten patients experienced significant stinging and pain at application site, two were protocol deviators, two severe adverse events (SAE) (death, hospitalization) (Table 4); (ii) patients were biopsy positive for basal cell carcinoma (BCC) at the end of treatment, three non-eligible patients were included in the intention-to-treat population erroneously and considered treatment failures, two were lost to follow-up, one SAE (death) (Table 4); (iii) patients were biopsy positive for BCC at end of treatment, one SAE (death) (Table 4)

significant overlying re-epithelialization associated with an underlying chronic inflammatory infiltrate and fibrosis at least to the level of the superficial reticular dermis.

Due to no standardization for the physicians global evaluation of response to treatment between centers, no statistical evaluation could be reached. Assessment of local irritation was more significant and marked in the Zycure than vehicle group, as 6 out of 62 patients in the Zycure group withdrew due to the severity of local irritation. Subjective assessment of the treated area for scarring at 6 months and 1 year showed no significant differences between treatment groups.

Table 5 Frequency and 95% confidence interval of treatment-related adverse events (AE) in intention-to-treat population

	Zycure ratio (%)	Vehicle ratio (%)
Population	62 (100.0)	32 (100.0)
Patients reporting ≥ 1 AE	57/62 (91.9)	22/32 (68.8)
AEs reported	286	133
95% confidence interval	81.5, 97.0	49.9, 83.3

Discussion

The ever-increasing prevalence of BCCs forms a significant impact on clinical practice not only in dermatology but also in plastic surgery and radiotherapy/oncology. Topical therapy for superficial BCCs is predominantly 5FU, although on review of literature there is lack of convincing evidence-based trial data and little information regarding clearance, clinical and/or pathological relapse rate.

An interesting observation was made in the paper by Moragas *et al.* in 1970. It was found that an intact epidermis impairs and in some cases prevents the absorption of 5FU explaining the poor results in nodular variants (up to 50% recurrence).[7]

Reymann in 1979[8] has shown that using a combination of curettage and subsequent 5FU treatments for nodular variants showed high recurrences on 10-year follow-up study.

Although systemic side-effects have not been reported, a review of topical therapy of 5FU by Goette *et al.* in 1981[9] outlines allergic contact dermatitis and photosensitization as local side-effects besides the irritation and soreness.

The more recent topical treatment tried has been 5% imiquimod cream. To date, preliminary data show encouraging treatment benefit for only with superficial lesions at low-risk sites after at least 4 weeks of therapy. Moreover redness and irritation are an inevitable side-effect.[10]

This study on the local cytotoxic activity of solasodine glycosides was primarily concerned with efficacy and safety

in BCCs. The mode of action of glycoalkaloids is still not clearly understood. There are two hypotheses in the literature. The first[11] suggests that steroidal glycosides interact with and disrupt the cell membrane, resulting in lysis of the cell. It is supposed that initial interaction is mediated either by specific receptors on the walls of the cell binding to the glycoside (sugar moiety) or through the binding of the compound to free sterols within the cell walls. The second hypothesis[12] suggests that the glycoside diffuses within the cancer cell, causing the expression of tissue necrosis factor (TNF) receptors by activation of the relevant genes. TNF receptors bind to TNF, commencing a cascade of reactions that cause cell death by apoptosis. Such diffusion is consistent with the suggestion that these compounds initially interact with free sterols (and in particular cholesterol) within the cell wall. Such interaction and diffusion is also consistent with the knowledge that the aglycone (steroid moiety) is highly lipophilic (although inactive).[11]

In any case, either explanation as to the initial interaction of the compound with cells is compatible with our clinical observations that some patients had regeneration of new epidermis at the application site within the first 4–5 weeks of treatment, despite continued twice daily application of Zycure; and that histological examination showed acanthosis of the regenerated epidermis on 8-week posttreatment biopsy.

These observations suggest that Zycure is at least partially preferential in its application to transformed cells.

Our findings favor the hypothesis of cell death by apoptosis (20% of ITT cases). Furthermore, these results clinically support the hypothesis that these compounds act preferentially in the lysis of transformed as opposed to normal cells.

We feel that this novel agent, Zycure, has overall efficacy, patient acceptance, low incidence of local adverse events and no systemic side-effects. While surgery may remain a more appropriate treatment for many patients, we feel treatment with Zycure may prove advantageous if there are multiple small tumors of recent onset and perhaps in these patients where the location of the tumor makes other therapeutic approaches difficult.

It would be interesting and informative to undertake some comparative studies with existing treatments to establish the practical use of Zycure in dermatology by case selection.

Conclusion

In the present study, we have shown effective clearance of skin tumors with Zycure compared to vehicle alone. Zycure treatment was well tolerated with no serious treatment related adverse events. We therefore feel that solasodine glycoside cream is a safe and effective alternative topical treatment for BCCs.

Further studies are required to investigate efficacy analysing different histological types and depths as well as different sites of BCCs.

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