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A Review of Solasodine Rhamnosides Therapy for In-Situ Squamous Cell Carcinoma on the Penis

Bill E. Cham[1*]

[1]Australasian Medical Research, Devil's Point Road, Republic of Vanuatu.

Author's contribution

The only author performed the whole review work. Author BEC wrote the first draft of the paper. Author BEC read and approved the final manuscript.

Review Article

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ABSTRACT

The majority of penile cancers develop from squamous cells within the skin resulting in a non-melanoma form of skin cancer, squamous cell carcinoma. Squamous cell carcinomas can develop anywhere on the penis, most appear on the foreskin in men who have not been circumcised or on the glans. Various types of squamous cell carcinomas ranging from Bowen's disease, erythroplasia of Queyrat and Buschke-Lowenstein tumour have been identified on the penis. When detected early, these types of cancer can be successfully treated. However, the current treatment procedures have the potential for disfigurement and dysfunction of male genitalia, with associated psychological distress. A relatively new class of antineoplastic agents, consisting of the solasodine rhamnosides, solamargine and solasonine, are very effective and safe for the treatment of a variety of skin cancers and show promise for the treatment of internal cancers. Here, three cases of distinct squamous cell carcinomas on the penis, Bowen's disease, erythroplasia of Queyrat and Buschke-Lowenstein tumour are reviewed which were successfully treated with a standard mixture of solasodine rhamnosides.

Keywords: Penile cancer; curaderm[bec5]; BEC; eggplant; solamargine; solasonine; squamous cell carcinoma; Bowen's disease.

**Corresponding author: Email: bill.cham@gmail.com;*

1. INTRODUCTION

Cancer of the penis is a rare disease in the United States and Europe, but is a major health problem in parts of South America, Africa and Asia. Incidence of squamous cell carcinoma (SCC) of the penis ranges from 0.4% of male genital cancers in the United States, to as high as 20% in China and Uganda [1-3].

In Europe and the USA, the overall incidence of penile cancer is 0.1 to 0.9 rising to 19 per 100,000 in some areas of Asia, Africa and South America. In the USA it is estimated that in 2013, about 1570 new cases of penile cancer will be diagnosed and about 310 men will die of penile cancer [4].

SCC in situ of the penis includes erythroplasia of Queyrat and Bowen's disease, which can progress to invasive SCC with the potential for metastases to the local lymph nodes and possibly to more-distant regions of the body resulting in potential fatality [5].

Bowen's disease and erythroplasia of Queyrat also known as SCCs in situ have a 10-30% risk to develop into invasive SCC in genital lesions [4-6].

Human papilloma virus infection has been reported in men with penile cancer. Additional risk factors include poor hygiene, smoking and phimosis [4-6].

Verrucous carcinoma is an uncommon form of SCC that can develop on male and female genitals; it can spread into surrounding tissues but rarely metastasizes [4].

The most common form of penile cancer is SCC. Due to the high risk for lymph node metastases, penile SCC is usually treated aggressively with Mohs micrographic surgery, excision with wide margins, or penectomy. These procedures have the potential for disfigurement and dysfunction of male genitalia, with associated psychological distress [5, 6]. Nonsurgical treatment options include cryotherapy, curettage with cautery, 5-Fluorouracil, radiotherapy, photodynamic therapy, laser therapy and topical imiquimod therapy. These treatment modalities appear to have similar efficacy and recurrence rates with no single therapy being superior for all clinical situations. They all have their advantages and they all have some side effects and adverse events. Some disadvantages of topical therapies for skin lesions are discomfort, burning, itch, redness, crusting, ulceration, erosion, weeping, flaking, vesicle formation, intolerable pain, and recurrence of the treated lesions and long duration of therapy. In particular, formulations of imiquimod must be applied for periods of weeks to months and fluorouracil for weeks. In addition, to the drawbacks of long duration of treatments and consequently prolonged local reactions, which lead to less-than-ideal adherence to therapy, one has to address the success rates. For example, treatment with various imiquimod formulations for up to 16 weeks resulted in clearances of 30.6% to 45.1% [7,8]. Fluorouracil cream applied for 1 to 4 weeks resulted in clearance of certain lesions ranging from 19.5% to 47.5% [9,10]. Thus, there is no single definite "right procedure" for all patients with SCC in situ. The choice of treatment should be guided by its efficacy, location and size of the cancer, number of lesions, availability of therapy, clinician expertise, patient factors, cosmetic outcome, cost and the patient's preference.

The glycoalkaloids solamargine and solasonine singly or in combination (BEC) have been shown to be good antineoplastic biological therapeutic agents [11-42]. The antineoplastic modes of action of these solasodine rhamnosides have been elucidated.

They are regarded as biological therapies, also known as targeted therapies that target the differences between cancer cells and normal cells. Malignant cells have specific rhamnose receptors that bind to the rhamnose sugar moiety of the solasodine rhamnosides [13,27,33, 37]. The solasodine rhamnosides are internalized into the cancer cells by receptor-mediated endocytosis. These glycoalkaloids then trigger extrinsic and intrinsic apoptotic pathways in cancer cells by up-regulating the expressions of external death receptors, such as tumour necrosis factor receptor 1 (TNFR-1), Fas receptors, TNFR-1-associated death domain and Fas-associated death domain. The solasodine rhamnosides enhance the intrinsic ratio of Bax to Bcl-2 by up-regulating Bax and down-regulating Bcl-2 and Bcl-xl expressions. These effects result in activation of Caspase -8, -9 and -3 in cancer cells leading to apoptosis of the targeted cell [15,29,30,33-37,44,45].

Normal, non-malignant cells do not possess the rhamnose binding protein receptor and are therefore not affected by therapeutic doses of the solasodine rhamnosides [11,12,33,35].

BEC is a standardized mixture of solamargine (33%), solasonine (33%) and di-and monoglycosides of solasodine (34%) [11,27,28,35,38-42].

Recently, a topical formulation Curaderm ^{BEC5}, containing BEC was introduced for the treatment of pre-malignant and malignant skin lesions. Topical therapy with Curaderm ^{BEC5} produces beneficial end results with a wide range of basal cell carcinomas (BCCs) and SCCs of varying locations and sizes ranging from millimetres to centimetres [11,27-29,35,38-42]. Cosmesis with little or no scar formation with Curaderm ^{BEC5} treatment are striking. Recently with periocular skin cancers, it was reported that the tissue-sparing technique of Curaderm ^{BEC5} also preserved functionality [44].

This report shows that Curaderm ^{BEC5} topical therapy is effective for the treatment of penile erythroplasia of Queyrat and Bowen's disease in humans. In addition it is shown that intralesion administration of BEC is effective for large multiple SCC lesions, verrucous carcinoma, on the glans and shaft of the penis of a horse.

1.1 Penile Erythroplasia of Queyrat

A 58 year old with an intra-epithelial SCC on the glans of his penis first noticed the lesion two years prior to consultation (Fig. 1a). He reported that the symptoms included pain, occasional bleeding and irritation. The prognosis by his dermatologist was partial or complete penectomy, which the patient refused.

Biopsy showed erythroplasia of Queyrat (Bowen disease on the glans of the penis), which is an in situ form of SCC (Fig. 1d) and is mostly seen in uncircumcised men.

The lesion was treated with topical Curaderm ^{BEC5} cream applied twice daily under occlusion. The patient was instructed to clean the area with a mild antiseptic, apply a coat of Curaderm ^{BEC5} cream, and cover the medicated area with a hypoallergenic micropore paper tape dressing.

Two weeks after commencement with Curaderm ^{BEC5} therapy, the lesion showed marked breakdown of the lesion tissue (Fig. 1b). At 6 weeks, the lesion was no longer clinically apparent, and the Curaderm ^{BEC5} treatment was stopped (Fig. 1c). A biopsy taken at the end of treatment period showed histologically that no residual cancer cells were present (Fig. 1e). Clinical assessment 5 years post treatment revealed that there was no recurrence. Side

effects during the treatment were limited to transient local irritation and ulceration; these resolved when new tissue had replaced the original lesions. Re-epithelialization of the treated lesion occurred whilst apoptosis and necrosis were in process. Thus, the dead cancer cells induced by Curaderm ^{BEC5} therapy were being replaced with normal tissue whilst cancer cells were being cleared by the treatment [11].

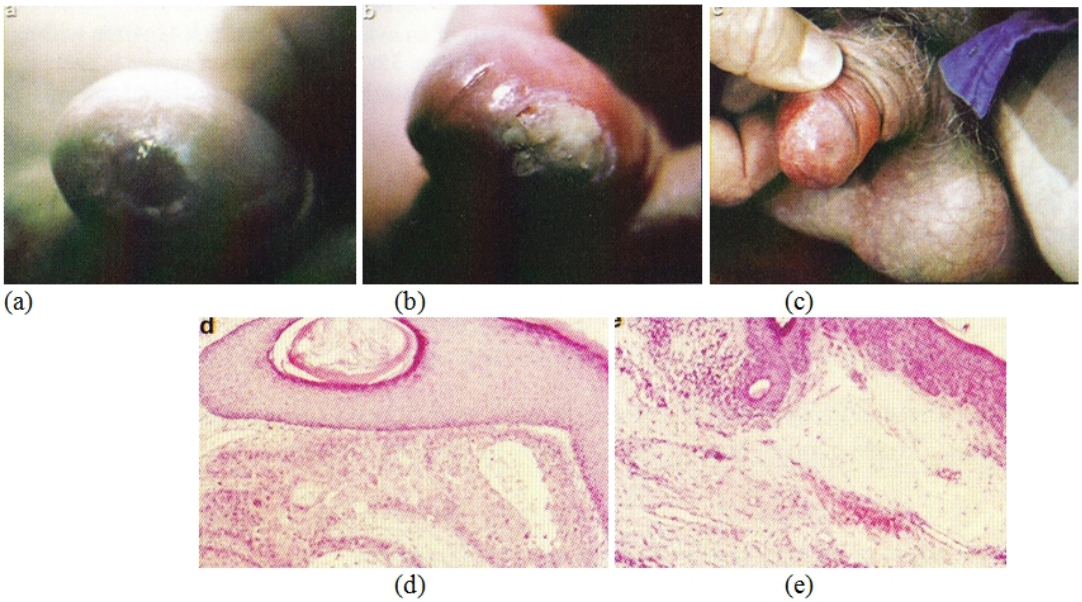

Fig. 1. An intra-epithelial SCC on the penis, diagnosed as penile erythroplasia of Queyrat, of a patient before (a), during (b) and after Curaderm therapy (c). The prognosis of this patient before treatment with Curaderm ^{BEC5} was glansectomy (amputation of the glans) with reconstructive surgery. Treatment period was 6 weeks. The clinical diagnosis was confirmed histologically by biopsy (d). After completion of the therapy histopathology determined that no residual cancer was present (e). Clinical assessment 5 years post treatment revealed that there was no recurrence

1.2 Bowen's Disease on the Penis

A 52 year old recently circumcised man was clinically (Fig. 2a) and histologically diagnosed with Bowen's disease on his penis. The SCC in situ was confined to the epidermis with adnexal involvement. Nuclear pleomorphism was moderate to marked, and mitotic figures were numerous. Dermal invasion was not present.

Previous treatment for this lesion consisted of two courses of topical 5% imiquimod cream for 2 years. Response was initially satisfactory, with clinical resolution, but the lesion returned 1 year after the completion of the second course of imiquimod treatment. The patient refused treatment with Mohs micrographic surgery because of the potential yet necessary, disfigurement and loss of function of the penis. The patient elected to be treated with Curaderm ^{BEC5} therapy. The treatment procedure was as outlined with Case 1 in this communication. Liquid nitrogen was used monthly only to reduce focal thickened verrucous lesions.

Two months after starting Curaderm ^{BEC5} therapy, the lesion showed minimal response (Fig. 2b). Marked clinical improvement was observed after 4 months, and by his 9th month follow-up visit, even greater regression of the erythematous macule was noted (Fig. 2c). At 10 months, the lesion was no longer clinically apparent, re-epithelialization of the treated area had occurred, and the Curaderm ^{BEC5} treatment was stopped. As with Case 1, the side effects during the treatment were limited to transient local irritation and ulceration; these resolved when treatment was discontinued. No clinical recurrence was observed over 2 years after completion of treatment with Curaderm ^{BEC5} therapy (Fig. 2d) [42].

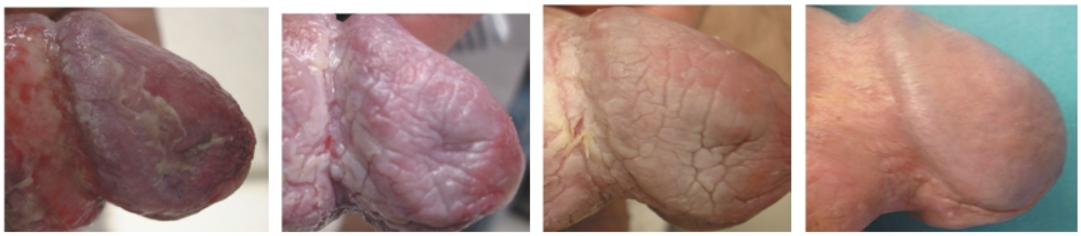

Fig. 2. Bowen's disease on the penis before treatment (a), two months after starting treatment with topical Curaderm ^{BEC5} (b), nine months after starting treatment (c), and two years follow-up after completion of treatment with Curaderm ^{BEC5} (d). Liquid nitrogen was used only to reduce focal thickened verrucous lesions and not for the Bowen's disease

1.3 Multiple Large Penile Cancers on the Glans and Shaft of a Horse

A pet horse of a veterinarian, approximately 15 years old, was presented with multiple clinically and histologically SCCs on the glans and shaft of its penis (Figs. 3a-c). The lesions were diagnosed as verrucous carcinomas on the penis, also known as Buschke-Lowenstein tumours. They comprise approximately 5% of all penile cancers in humans and represent a special variant of SCC. They are well differentiated and do not metastasize, but spread aggressively by local extension and may destroy penile tissues entirely if left untreated. The horse had these lesions for approximately one year. The estimated weight of these multiple lesions ranged from 5-100g. A sterile solution of 10%, w/w, of BEC in dimethylsulfoxide, was used to treat these cancers by intralesion injections.

The doses injected intralesionally were 100mg BEC per 1kg tumour weight. Thus, for a tumour weight of 100g the dose was 0.1mL of the 10% BEC solution. Each injection was done intralesionally on multiple sites of each tumour mass.

General anaesthesia was required prior to multiple injections in each tumour. The horse was injected with BEC solution once a week for 3 weeks. Fig. 3d shows the intralesion injections into each individual tumour mass with BEC solution. Massive haemorrhagic necrosis of the tumour masses occurred during the 3 weeks treatment courses (Figs. 3e and 3f). After the final treatment (3d set of injections), a large tumour separated entirely and fell off while the horse was waking up from the anaesthetic (Fig. 3g). Figs. 3h and 3i show the successfully treated penis with no clinical signs of any tumour 3 months after the treatment of the cancers with the BEC solution. The horse was in excellent condition after treatment (Fig. 3j). There were no recurrences of the tumours after 5 years follow-up [29].

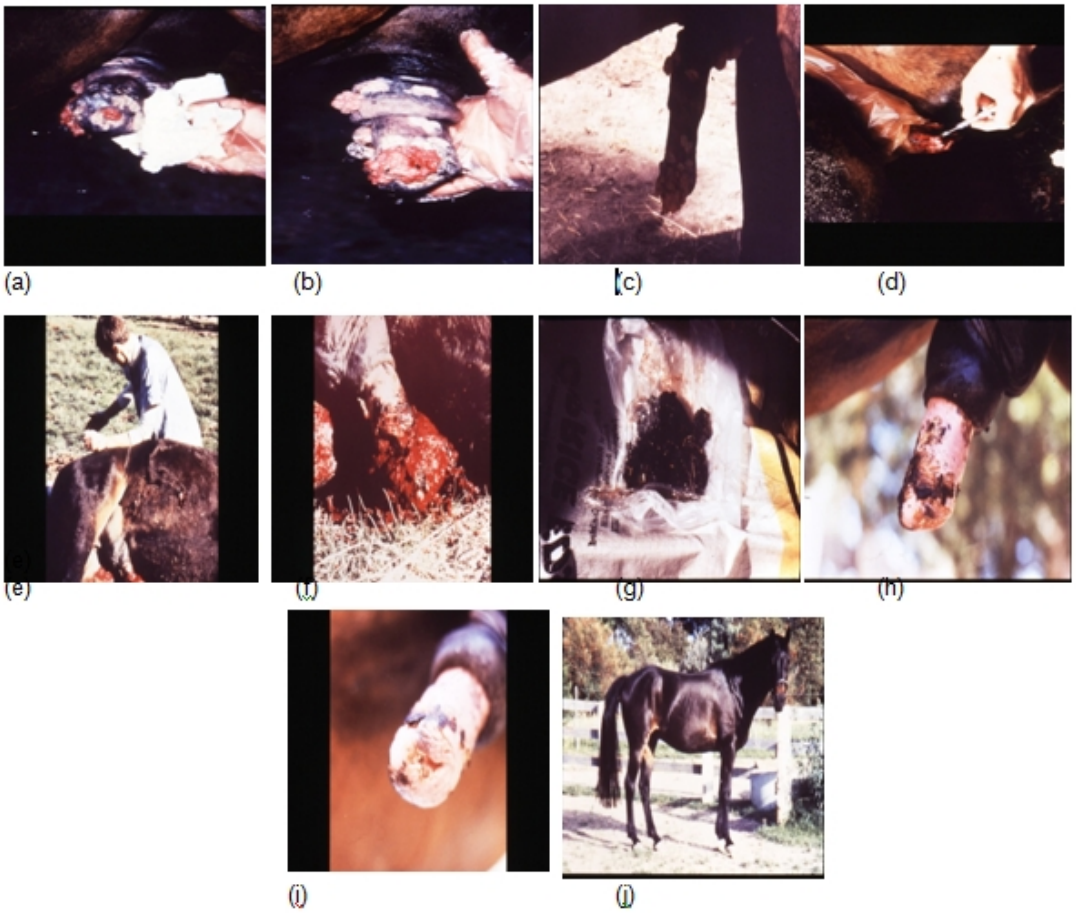

Fig. 3. Multiple large SCCs on the penis of a horse, diagnosed as verrucous carcinomas, also known as Buschke-Lowenstein tumours. This horse was given three courses of BEC injections before complete remissions of all the tumours were achieved. The extent of multiple lesions are seen in (a) and (b). (c) shows that the tumours were extended throughout the entire penis. The veterinarian injected each individual tumour mass with BEC (d). The horse needed general anaesthetic during BEC therapy. Massive haemorrhagic necrosis of the tumour masses occurred during the treatment course, (e) and (f). After the final treatment (third injection) a large tumour separated entirely and fell off while the horse was waking up (g). Successfully treated penis showing no signs of any tumour (h) and (i) two years after the initial diagnosis and treatment of the cancer. The horse was in excellent condition after treatment (j)

2. DISCUSSION

Penile cancer usually originates in the glans with the prepuce and shaft being the other common sites. Delay in diagnosis occurs because the significance of the lesion was initially not appreciated and the patient delays medical examination due to a variety of reasons including fear, guilt, embarrassment or ignorance.

SCC in situ of the penis includes erythroplasia of Queyrat and Bowen's disease, both of which can progress to invasive SCC with the potential for metastases to the local lymph nodes and possibly to more-distant regions of the body. Progression to SCC is more common in erythroplasia of Queyrat than in other forms of Bowen's disease of the penis. Progression of penile erythroplasia of Queyrat to invasive carcinoma may occur after a variable period in 10-33% of cases [4].

It is therefore important to have a safe and effective treatment for these conditions before they metastasize.

Mohs micrographic surgery is currently considered the surgical treatment of choice for Bowen's disease of the penis with the best possible cure rate, maximal tissue sparing, and complete margin control. Several nonsurgical treatment options exist, with varying degrees of efficacy and recurrence risks. These include cryotherapy, curettage with cautery, 5-Fluorouracil, radiotherapy, photodynamic therapy, laser therapy and topical imiquimod therapy. Potential scarring, low success rates, high recurrence rates, long duration of treatment and prolonged local reactions are some major drawbacks with current treatments [46] as was shown with the Case 2 patient in this communication, who was treated over 2 years with imiquimod, with initial clinical resolution, but with recurrence in 1 year.

The glycoalkaloids solamargine and solasonine singly or in combination (BEC) are known to be good antineoplastic biological therapeutic agents. These chemical compounds occur in plants of the Solanaceae family such as S. linnaeanum (devil's apple) and S. melongena (eggplant) [12,43-46]. At therapeutic doses, they induce apoptosis in cancer cells but not in normal cells. This phenomenon explains that whilst on BEC therapy, cancer cells are cleared and are concurrently replaced with normal cells resulting in little or no scarring. Unlike other chemotherapeutic agents, BEC eliminates cancer cells whether they are proliferating or not.

Many topical chemotherapy studies with BEC for keratosis, keratoacanthoma, basal cell carcinoma, and cutaneous squamous cell carcinoma on the face, trunk and extremities have been published [11,27-29,35,38-46].

Complete histological and clinical regressions have been reported, with no clinical recurrences 1 to 10 years after treatment. Reported side effects during treatment were erythema, pruritis, burning, and swelling of and around the treated lesions. These side effects were transient and lasted for several minutes after application of Curaderm ^{BEC5}. The side effects were shown to be due to the keratolytic agents salicylic acid and urea in the Curaderm ^{BEC5} formulation. The active ingredient BEC showed no side effects [46].

The rapid efficacious response of this antineoplastic biological therapeutic agent BEC is shown with Case 3. Three courses of intralesion injections into the tumours over a 3 weeks period resulted in the rapid clearance of multiple large tumours on the penis. Similar observations were seen when large chondrosarcomas of 500g were eliminated with only 2 injections of BEC. Two administrations of BEC applied intralesionally also cleared large melanomas, BCCs and SCCs [11,29,35,43-45].

The common observation, whether BEC was applied topically as a cream formulation or injected intralesionally as a solution, is the very impressive cosmetic outcome. The tissue-sparing and preservation of functionality of BEC therapy reported here, and previously

shown with periocular skin cancers [44] treated with Curaderm ^{BEC5} place BEC therapy in a special category.

3. CONCLUSION

BEC therapy in different formulations and by different administrations results in the successful treatment of SCC of the penis with little side effects. Long-term follow-up periods after treatment with BEC show no recurrence. The resulting cosmetic effect after treatment is excellent. The BEC treatment procedure is tissue-sparing and preserves functionality, and may be the elusive alternative to other more-destructive treatment options, for in situ SCC on the penis. Further and larger prospective studies with long-term follow-up are required to verify the efficacy and safety of solasodine rhamnosides in treating penile cancers.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Professor Bill Cham holds patents on BEC.

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