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Photodynamic therapy for Bowen's disease and squamous cell carcinoma of the skin

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KEYWORDS

ALA-Aminolevulinic acid;
SCC-Squamous cell carcinoma;
PDT-Photodynamic therapy;
Bowen

Summary

Background : Photodynamic therapy involves the activation by visible light of a previously administered photosensitizing agent in order to cause tumor necrosis. Skin tumors can be treated with topical photosensitizers and thus avoiding systemic side effects. In this study we evaluate the immediate and long-term effects of photodynamic therapy (PDT), using aminolevulinic acid (ALA) as a photosensitizer and a non-laser light source, on Bowen's disease (intra-epithelial squamous cell carcinoma) and on frank squamous cell carcinoma (SCC) of the skin.

Methods: ALA in cream form (20%) was topically applied on biopsy-proven Bowen's disease or SCC of the skin. The lesions were covered with occlusive and light-shielding dressing. Sixteen hours later, they were submitted to a 10-min light session using Versa-Light™, a non-laser light source (spectral output of 580–720 nm and 1250–1600 nm, 100 J/cm²). The initial evaluation was done 21 days post-treatment and every 3 m thereafter. Patients that did not respond to treatment after two to three sessions were referred to surgery.

Results: Forty Bowen's disease lesions (24 patients) and 43 SCC lesions (18 patients) underwent treatment. Median follow-up was 21 ± 8 m. No patient had any remarkable side effects. Thirty-four Bowen's disease (85%) lesions completely responded as did 32 SCC lesions (74%).

Conclusions : Our findings showed that PDT is highly effective in treating Bowen's disease and SCC lesions and can be used as a first treatment modality in so far as its use does not preclude the subsequent surgery recommended for the small percentage of failures.

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Introduction

Non-melanoma skin cancer is the most common form of cancer among Caucasians [1]. Squamous cell carcinoma (SCC) arises from keratinocytes of the epidermis. It is less common than basal cell carcinoma (BCC) but it is more destructive because it can invade surrounding tissue and metastasize more readily. Bowen's disease is a persistent, progressive, red, scaly or crusted plaque, which is due to an intra-dermal carcinoma and is potentially malignant [2].

There are several treatment modalities for SCC and Bowen's disease. These include interventions such as conventional surgery, Mohs' surgery and cryosurgery, as well as non-surgical procedures such as radiotherapy and topical chemotherapy. Surgical excision is the definitive treatment but may not be practical in patients with numerous or large lesions, or lesions in anatomically difficult areas such as the nose and ear.

Photodynamic therapy (PDT) involves the use of photosensitizing drugs, such as hematoporphyrin derivatives, in conjunction with light for the treatment of tumors [3]. The systemic use of hematoporphyrin derivatives, however, has several disadvantages: it is not a chemically pure compound and also one that is chemically unstable [4], it is not highly selective to tumor tissues and it is slowly cleared from the skin, a characteristic which leads to side effects such as skin sensitivity [5].

Malik and Lugaci [6] proposed a model for selective destruction of proliferating cells by stim-

ulation of endogenous porphyrins synthesis in response to light exposure. Topical application of 5-aminolevulinic acid (ALA) stimulates protoporphyrin synthesis in tissues [7]. ALA is an endogenous porphyrin precursor that stimulates the synthesis of protoporphyrin IX [8]. It has been shown that protoporphyrin IX is a highly effective photosensitizer, and that PDT by means of ALA leads to cell destruction [9].

In 1990, Kennedy et al. [9] reported the first treatment of BCC and SCC using topical ALA-PDT with a complete response of 75% for SCC patients. Since then, several authors reported their results from the use of ALA-PDT in both skin SCC and in Bowen's disease [9–14]. They used different light sources, among them argon dye, Nd:Yag or copper vapor-dye lasers, and tungsten or xenon lamps.

We now report our experience in using PDT for the treatment of SCC and Bowen's disease using topical ALA and a non-laser light source based on a Xenon lamp.

Methods

Study protocol

The study was approved by the local Helsinki Committee and by the Ministry of Health (protocol number HT40). Inclusion criteria were pinch biopsy-proven Bowen's disease or SCC of the skin. Exclusion criteria were known porphyria or any photosensitivity.



Figure 1. Squamous cell carcinoma of the skin of lower limb prior to PDT.



Figure 2. Same lesion 3 weeks after PDT.

The diameter of the lesions was measured before the treatment and during follow-up. A cream of aminolevulinic acid (20%) was prepared at the hospital pharmacy within 24 h prior to application and applied onto the lesion after cleaning the area and removing any crusts. Approximately 0.2 ml of the cream was applied to the lesion including 0.5 cm of the skin around it, which was then covered with an occlusive and light-shielding dressing. Sixteen hours later, the lesions were exposed to light at 100 J/cm^2 for 600 s (100 mW/cm^2). A routine clinical evaluation, including picture taking of the lesions, was performed 21 days after the treatment and every three months thereafter. The results of the treatment were evaluated according to the following criteria: complete response (CR, clinical tumor disappearance), partial response (PR, more than 50% reduction of tumor diameter) and no response (NR, less than 50% reduction of tumor diameter).

Photosensitizer

5-Aminolevulinic acid was purchased from Finetech Ltd. (Technion City, Haifa, Israel) as powder with a purity of 98%. The cream contained 20% ALA in a base ointment.

Light source

A Versa-Light (ESC Medical Systems Ltd., Yokneam, Israel) illuminator, which uses a xenon lamp as the light source and fiber optics as the light delivery system was used for treatment. The spectral output of

Table 1 The locations of the tumors treated with ALA-PDT.

Location	Bowen's disease	Squamous cell carcinoma
Face (n)	11	10
Scalp (n)	14	21
Trunk (n)	2	1
Limb (n)	13	11
Total (n)	40	43

this system is limited to two wavelength bands of 580–720 nm (92%) and 1250–1600 nm (8%). It had been previously shown to be effective in experimental studies as well as in the treatment of patients [15–18].

Study cohort

The study cohort consists of 24 patients (11 women and 13 men) who had 40 Bowen's disease lesions and 18 patients (8 women and 10 men) who had 43 SCC lesions. Their average age was 75 ± 10 years (range 49–93 years). The location of the different tumors is shown in Table 1. The average diameters of the SCC and Bowen lesions were 1.4 ± 0.8 cm (range 1–3 cm) and 1.6 ± 0.9 cm (range 1–4 cm), respectively.

Results

The treatment was well-tolerated by all the patients without local anesthesia. Mild-to-strong

stinging or burning sensations were reported at the site of the treated areas during but not following exposure to the light. The treated lesions generally became erythematous and edematous during or immediately after therapy and healed within 2–3 weeks. The exposed areas of adjacent skin showed only a mild reaction to the treatment which healed within a few days.

The response of the tumors to the topical PDT after application of 5-ALA is summarized in Table 2. Complete response was observed in 85 and 74% of Bowen's and SCC lesions, respectively (Figs. 1–4). Analysis of the response to PDT by size or location of the lesion was of no significant difference (data not shown). The cosmetic result was very good and

Table 2 Number of treatments and tumor response to ALA-PDT.

	Bowen's disease	Squamous cell carcinoma
Treatments (<i>n</i>)		
1	24 lesions	32 lesions
2	13 lesions	3 lesions
3	3 lesions	8 lesions
Tumor response		
CR	34 (85%)	32 (74%)
PR	1 (2.5%)	7 (16%)
NR	5 (12.5%)	4 (10%)

CR, complete response; PR, partial response; NR, no response.



Figure 3. Bowen's disease of forehead prior to PDT.



Figure 4. Same lesion 3 weeks after PDT.

there were no long-term effects on the normal skin. Treatment was repeated in cases of partial tumor response after a single PDT session. Tumors that had partial or no response to treatment after two to three sessions were referred for surgical excision.

The median follow-up was 21 ± 8 m. There were two recurrent Bowen's lesions, which completely responded after the second PDT.

Discussion

At the beginning of the 20th century, von Tappeiner introduced the term "photodynamic therapy" for oxygen-dependent destruction of tissue after photosensitization and subsequent irradiation with light [19]. He also pioneered the attempt of applying photodynamic therapy of skin tumors using a 5% solution of eosin dye for topical treatment in a 70-year-old woman with a SCC lesion of the face. The tumor area was repeatedly painted with the dye over a period of 2 m during which the patient was exposed to either sunlight or lamp-light. This therapeutic regimen resulted in tumor regression with an excellent cosmetic result [20].

5-Aminolevulinic acid is a precursor of protoporphyrin IX (Pp IX) in the biosynthetic pathway of heme. In certain types of cells and tissues, the rate of synthesis of Pp IX is determined by the rate of synthesis of ALA which, in turn, is regulated via a feedback control mechanism governed by the concentration of free heme. The presence of exogenous ALA bypasses the feedback control, and thus may induce the intracellular accumulation of photosensitizing concentration of Pp IX [8,9]. Since ALA in aqueous solution is able to penetrate abnormal but not normal keratin, it can selectively pass through the damaged keratin of BCC and Bowen's disease lesions [8,9].

Our results of treating Bowen's disease and SCC lesions by PDT are encouraging. Many of these lesions are present in elderly ill patients who are not uncommonly at high risk for surgery. This technique with ALA cream and superficial light illumination offers a usually single outpatient treatment with good results and without side effects.

The outcomes of clinical studies on PDT for skin tumors are generally difficult to compare, since different variations of PDT protocol were used. All the reported studies used 20% ALA in various cream formulations: some used ALA alone [21] and others add dimethylsulfoxide (DMSO) and edetic acid disodium salt (EDTA) to the ALA cream [22,23]. In most of the studies, light was applied from 3 to 8 h after

topical ALA application. We applied light 16 h after the ALA application in accordance with the findings of Szeimies et al. [24] who showed a strong correlation between application time of ALA and the occurrence of protoporphyrin IX fluorescence in tissue tumors. At 4 h following ALA application, only skin appendages demonstrated fluorescence typical of protoporphyrin IX; after 12 h, fluorescence was detectable in tumor cells in deep dermis [24].

Different light sources have been used for PDT. Several groups performed irradiation with laser emitting wavelengths of 630 or 635 nm [11,14,24], while non-coherent light sources have been used for PDT by others [7,8,10,23]. Since coherence of light is not necessary for PDT, an incoherent light source offers the advantages of being less expensive and easier to handle. In addition, non-coherent light sources emitting both 635 and 670 nm radiation could improve the efficacy of PDT, because the two main photoproducts of PpIX, the photoporphyrins "A" and "B", can be activated by light at about 670 nm [25]. It has been suggested that the excitation light for dermatological application of ALA PDT should consist of a broad band of 600–700 nm or even 550–700 nm [21] such as the light source that had been used in the present study.

Our results fit the published data for ALA-PDT for Bowen disease and SCC of the skin. ALA-PDT treatment cleared 86–93% of Bowen's lesions; the average recurrence rate was 12% (ranging from 0 to 40%) during follow-up periods of 3–36 m. Most of these studies were small with only 3–10 lesions. These studies used different light source including laser or xenon lamp [26]. The reported response rate for ALA-PDT to SCC is 54–100% with average recurrence rate of 24% after 3–47 m [26].

The light source that we used in this study, Versa-Light, fulfills the requirements of light sources for performing PDT. It has a broad band spectral emission in two wavelength bands of 580–720 nm and 1250–1600 nm, closely matching the absorption spectra of existing photosensitizers. It has a sufficient power flux to match the output of expensive laser systems. It is contained in a small, tabletop unit and is easily transportable. It requires no special electrical or cooling installations. It is considerably less costly than a laser system, and its operation and maintenance is simple.

Our findings showed that PDT is highly effective in treating Bowen's disease and SCC lesions and can be used as a first treatment modality so far as its use does not preclude the subsequent surgery recommended for the small percentage of failures.

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