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Methyl aminolevulinate-based photodynamic therapy of Bowen´s disease: Observational study of 21 lesions

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ABSTRACT

Background: Although surgical removal is the treatment of choice in Bowen's disease (BD), there are cases in which by age, comorbidities, use of anticoagulants, location, cosmetic result, or size, it is preferable to use other treatments such as cryotherapy, 5-fluorouracil cream, imiquimod 5% cream or photodynamic therapy (PDT). Efficacy of PDT in BD is supported by substantial research and clinical data.
Objectives: This study aimed to evaluate the long term effectiveness of methyl aminolevulinate-PDT (MAL/PDT) on a wide range of Bowen lesions in different locations and sizes.
Methods: Patients diagnosed with BD were treated in 3 sessions with a 4-week interval in between with MAL/PDT between January 2016 and January 2017 in a private clinic. Clinical response and relevant patient and tumour characteristics were analyzed during the first year after start of the PDT sessions.
Results: In total, 21 BD lesions in 18 patients were included in the study. Complete regression (CR) after 3rd PDT session was 87.5% and 100% at the 6-month follow-up. Treatment was well tolerated and local adverse reactions were very scarce. No recurrence was observed at 12-month follow-up. Cosmetic outcome at 12 months was good or excellent in 100% of patients.
Conclusions: MAL/PDT is an effective, non invasive and safe treatment modality for BD with excellent cosmesis.

1. Introduction

Surgical excision is the gold standard therapy for non-melanoma skin cancer (NMSC), the most frequent skin tumour in the Caucasian population [1,2]. A type of superficial NMSC is the Bowen's disease (BD) that is currently considered as a squamous cell carcinoma in situ. The lesions are macular, polycyclic, erythemato squamous, yellowish-brown, well demarcated (from a few mm to several cm) with an irregular border, on the skin exposed to the sun, usually in people over 60 years of age, being more frequent in women [3]. Diagnosis of BD tends to be delayed because they appear asymptomatically and often mimic benign skin conditions such as actinic keratosis, eczema or psoriasis, but BD lesions are much more stable and do not respond to treatment with corticosteroids. Patients with BD have an excellent prognosis because BD is a slow-growing disease and generally responds favorably to treatment. Although BD lesions are not life threatening, there is a small risk (˜3%) of progression to invasive squamous cell carcinoma [4].

BD is still a challenge for the dermatologist when it occurs in form of multiple or large lesions, especially if arising in sites of high cosmetic importance. Although surgical excision is the standard treatment, some patients may be unsuitable candidates for surgery because of their poor general health status. In addition, surgical excision may be undesirable in some cases because of the likelihood of functional loss or cosmetic disfigurement due the location or size of the lesion [5]. In these cases, dermatologists may consider cryotherapy, topical treatment with 5-fluorouracil or imiquimod and light therapies such as Photodynamic Therapy (PDT) [6,7]. Since BD is a lesion that affects the pilosebaceous unit, the treatments must reach enough depth to offer complete eradication. For small lesions, cryotherapy with or without previous curettage is recommended. However, some extensive or localized lesions in areas of difficult healing, such as the legs, often represent a therapeutic problem, with PDT being the most effective treatment. In addition, subclinical lesion can be PDT treated with the potential to slow and possibly prevent the development of new lesions.

PDT acts through the selective destruction of atypical keratinocytes by the accumulation and then photoactivation of a photosensitizer (PS). Generally, in the treatment of BD by PDT, the precursors of PpIX, such as the 5-aminolevulinic acid (ALA), and its derivatives, such as the lipophilic agent methyl aminolevulinate (MAL), are the PSs most frequently used [8,9].

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Although the efficacy of MAL/PDT in BD is supported by substantial research and clinical data [9–14] it should be interesting to evaluate the effectiveness over time of MAL/PDT on a wide range of Bowen lesions in different locations and sizes.

2. Materials and methods

2.1. Patients

In this clinical trial, patients diagnosed with BD were treated with PDT in a private clinic between January 2016 and January 2017. The end date was chosen to ensure at least 12 months of follow-up after the patient had received treatment. An informed consent was signed prior to inclusion. Participants were selected according to the following inclusion criteria: i) having been diagnosed with BD by means of a biopsy of the most representative lesion, thus confirming the clinical diagnosis by histopathology, ii) tumour characteristics as size and location on cosmetic sensitive areas, iii) patients characteristics: advanced age, use of anticoagulant, etc... Exclusion criteria were: i) under 18 years of age, ii) immunosuppressed, iii) contraindications for the use of MAL for presenting porphyria or photodermatosis that could influence the objectives of the study, iv) intolerance to any ingredient of the MAL formulation, v) other topical treatments within the treatment area were not allowed for 12 weeks prior to the start of the present study, vi) no topical treatments were allowed that could possibly affect the response to the study treatment, and vii) BD in the anogenital region due to its different aetiology and known higher recurrence rate. Table 1 shows the baseline characteristic of the 18 treated patients.

2.2. Study design

A schematic picture of the study protocol is showed in Fig. 1.

Prior to PDT treatment, histological assessment by means of punch biopsy was carried out. Photographs were taken before PDT and each follow-up (0, 1, 2, 3, 6 and 12 months), together with routine clinical processes (visual inspection and palpation). Clinical efficacy was quantified by means of 3-point scale: complete regression (complete absence of any clinical sign indicative of BD) (CR), partial regression (PR) and no regression (NR) with a regression percentage of respectively 100%, 25–99% and 0–24%. As we did not carry out a histological demonstration of BD clearance at the end of the period of evaluation (6-month follow-up), we considered an adequate long-term clinical follow-up of patients (at least 12 months), in accordance with the most used oncological evaluation and treatment for non-melanoma skin cancers [15]. Only biopsy was done when the possibility of recurrence was suspected.

Table 1
Baseline characteristics of the treated patients.

Patients n = 18
Men, n (%): 9 (50)
Women, n (%): 9 (50)
Mean age (± SD); range, median: 74.8 ± 10.3; [56-87]; 76.5
Number of lesions/patient, n (%)
1: 16 (88.9)
2: 1 (5.6)
3: 1 (5.6)
> 3: 0 (0)
Total number of lesions: 21. Lesion location, n (%)
Face (cheek, forehead, ear, nose,…): 13 (61.9)
Trunk/neck: 2 (9.5)
Upper extremities: 2 (9.5)
Lower extremities: 4 (19.0)
Lesion mean diameter (mm); range; median: 18.57 ± 10.51; [10-50]; 20
Range, n (%)
1-10mm: 9 (42.9)
11-20mm: 8 (38.1)
21-30 mm: 2 (9.5)
> 30 mm: 2 (9.5)
Number of sessions
3:18 (100)

2.3. Treatment protocol

A 1 mm thick layer of methyl aminolevulinate (MAL) 16% (Metvix®, Galderma, Lausanne, Switzerland), extended up to 5 mm within the surrounding healthy skin, was applied under occlusion. Before application of MAL, the lesions were prepared by surface debridement with a curette with the aim to only remove crusts and scales. Next, after 3 h as a period of incubation, the excess cream was wiped off and lesions were illuminated with a red light-emitting diode (optimum wavelength 630 nm, 75 J/cm^2; exhibition time of 10 min; Aktilite® CL128, Galderma, Lausanne, Switzerland). Patients were instructed to avoid intense sunlight for approximately 48 h after treatment and not be exposed to intensive ultraviolet radiation during the course of the study.

Lesions were irradiated during three treatment sessions with 4 weeks in between each PDT session for a complete treatment cycle (Fig. 1). Diprogenta® was used only in the case of inflammation and clorhexidine in the case of appearance of wounds. Before exposure to light the cream was removed using a swab and the red fluorescence of porphyrins was visualized with a Wood´s light. A photograph was then taken before starting light exposure (Fig. 2).

2.4. Safety and tolerability of the treatment

Local adverse reactions at the application site (erythema, oedema, crusting, burning sensation, vesicles, hematoma, infection, pigmentary changes –hypo or hyperpigmentation- and scarring) were documented immediately after PDT. In addition, pain during PDT was evaluated with a visual scale (VAS) of 100 mm, from 0 mm (no pain) to 100 mm (severe pain). Cosmetic outcomes were scored using a four-point sale (excellent: no significant changes; good: minor changes; poor: serious hypo- or hyperpigmentation and/or visible scarring; very poor: important scarring).

3. Results

Between January 2016 and January 2017, 20 patients with BD hystopathologically diagnosed were treated by PDT. Two lesions corresponding to two patients were located in the anogenital region and thus they were excluded for further analysis. Finally, 21 BD lesions in 18 patients were included in the study. None of the patients were immunocompromised.

Most of the lesions were located on the face (n = 13). The remainder were located on the extremities (n = 6) and neck (n = 2) (Table 1). Mean lesion size was 18.57 ± 10.51 mm, and ˜81% were ≤ 20 mm (Table 1).

The clinically verified complete response rate of lesions after 3rd session was 87.5% (16/18). In the following 4 months healing process still took place, and thus at 6-month follow-up CR was 100% (Table 2). Recurrences were not observed during the period evaluated. No patient showed progression of the BD to invasive squamous cell carcinoma (SCC). Fig. 2 shows two lesions of Bowen in different locations delineate with the Wood´s lamp and their disappearance at 6-month follow-up. After the 3rd PDT session no lesion exhibited fluorescence.

Local adverse reactions were very scarce and they were dependent on the size and location of the lesions, with erythema being the most frequent immediate side effect followed by burning sensation and some oedema, crusting, scarring and pigmentary changes as slight hypopigmentation. While this last side effect took place after the 3rd MAL/PDT session, the other adverse reactions were observed just after the 1st MAL/PDT session. VAS scores were from 30 mm to 50 mm, with a mean valor of 38.1 ± 8.7 mm; thus, little low pain perception was reported

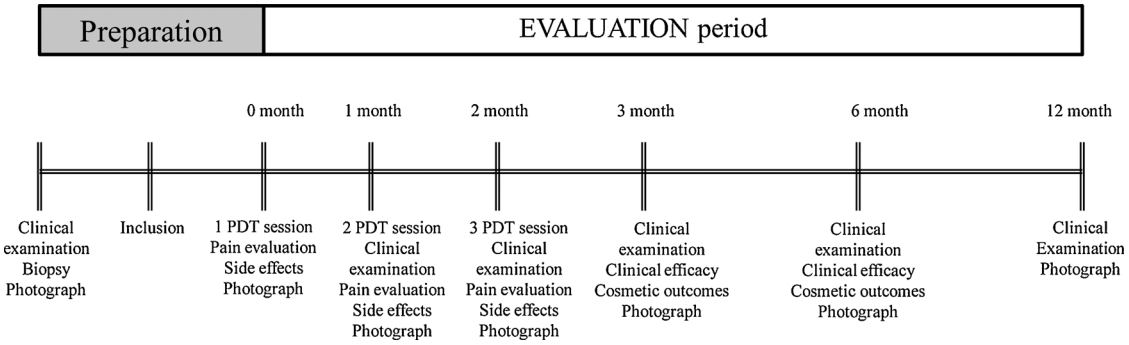

Fig. 1. Schematic study design.

by the patients. The highest values scores were reported mainly by patients with lesions in the cheek (Fig. 3). Cosmetic outcomes were good 2/18 (12.5%) or excellent 16/18 (87.5%) after the 3rd MAL/PDT session. In addition, at both 6 and 12 month follow-ups, all patients showed excellent cosmesis.

Table 2
Clinical efficacy.

Nº of patients	After 3rd PDT session	6-month follow-up	12-month follow-up
2	PR	CR	CR
16	CR	CR	CR
% CR	87.5	100	100

4. Discussion

Topical PDT has been approved for the treatment of BD and its use is increasing because of the generally favorable efficacy and low adverse effects profile. PDT allows simultaneous treatment of multiple tumors and incipient lesions, relatively short healing times, good patient tolerance, and excellent clinical and cosmetic outcome [16]. Photosensitizing agents used are methyl aminolaevulinate (MAL) Metvix® or BF-200 ALA (Ameluz®). ALA is hydrophilic whereas MAL is more lipophilic, and hence MAL may penetrate more deeply into lesions; however, these agents when used in the treatment of actinic keratosis (AK) and nodular superficial basal cell carcinomas (BCC) failed to show a difference in response [17,18]. Previous studies seem to demonstrate that ALA causes more pain sensation that MAL in AK [17,19]. Recently, some higher efficacy has been obtained by ALA in comparison with MAL in 27 BD lesions, having been found 89% clinical response rates (CRR) with ALA and 78% with MAL [20].

Although Protoporphyrin IX has absorption peaks at 410 (the largest peak), 505, 540, 580 and 630 nm, most light sources for PDT use the 630 nm red absorption peak, to improve tissue penetration. In addition, fractionation (discontinuous illumination) can improve the results by allowing tissue reoxygenation during “dark” periods. The two-fold irradiation scheme involved a low initial fluence rate followed by a higher fluence rate. Nevertheless, it should be pointed out that a previous study did not find superior results in BD by the fractionation of the conventional illumination [21].

The usual protocol for MAL/PDT in BD is double therapy 7 days apart, repeated at 3 months, if required [6]. Based in the published results obtained mainly after the use of 1 cycle of MAL/PDT (2 sessions 7 days apart) using red light (˜630 nm) at a dose of approximately 37 J/cm^2 [10–132223], we decided to apply 3 sessions (˜630 nm; 75 J/cm^2) spaced 4 weeks in order to limit side effects and guarantee CR. In 2016 the American Society of Dermatologic Surgery recommended 2–3 sessions of MAL/PDT using red light (˜630 nm; 75 J/cm^2) for BD treatment [24]. The protocol here designed conforms to these guidelines [24].

Patients with BD treated with PDT should be monitored after treatment due to the risk of incomplete response and recurrence. A significant risk factor for unsuccessful treatment is large lesion size (> 20 mm) [12,25–27]. Regarding the number of PDT sessions, it is well known that two or more sessions are superior to one [21,25,27]. In addition, worse results were observed in immunosuppressed patients [14,28]. As the effectiveness of PDT is mediated to some extent by the body´s immune system, this can be translated to increased recurrence rates (RR) in immunocompromised population, so that PDT is not a first-line recommended in immunocompromised patients [15].

Recurrence in the case of large lesion sizes (> 20 mm in diameter) after a single MAL/PDT session with red light of 630 nm at 37 J/cm^2, is common [12]. On the other hand, data published show successful CR

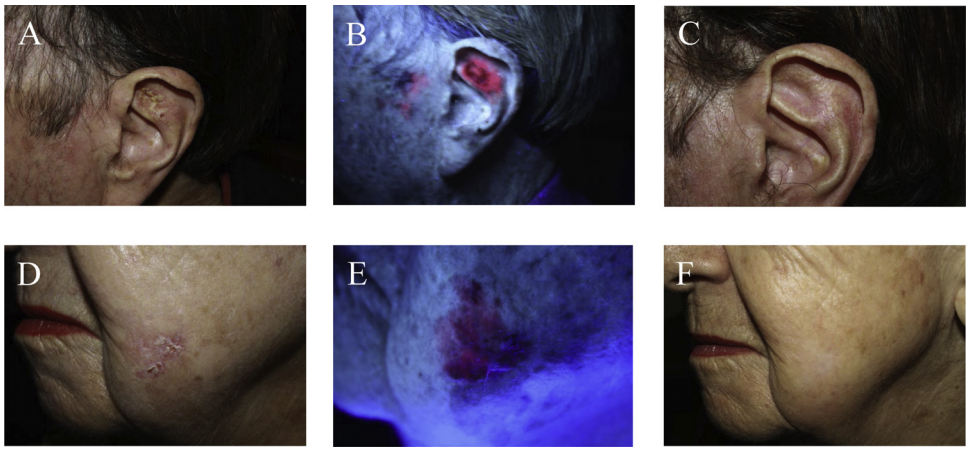

Fig. 2. BD in the ear (A), delineated lesion by Wood´s lamp before PDT (B), complete regression four months after 3rd PDT (C); BD in the cheek (D), delineated lesion by Wood´s lamp before PDT (E), complete regression four months after 3rd PDT session (F).

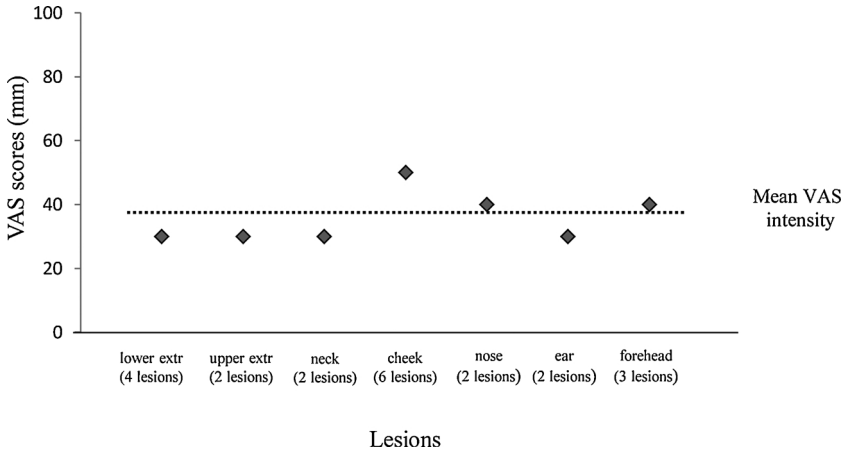

Fig. 3. Visual analog scale (VAS) scores during PDT sessions in function of the kind of lesion treated.

with one or two MAL/PDT sessions on lesions with sizes ≤20 mm in diameter by irradiation with 630 nm light at a fluence of 37 J/cm^2 [12]. In this work we report a CR of 100% after 6-month follow-up. We carried out 3 sessions applying MAL over lesions with an average size of 19 mm and irradiating with red light at 75 J/cm^2, which would corroborate that both an additional session and an increase of the fluence of the light used, serves to ensure success of the treatment and minimize recurrences. We detected skin surface fluorescence by using a simple handheld Wood`s lamp, which allows us delineate lesions and is helpful in identifying persistent/recurrent disease.

From an aesthetic point of view, the location of the lesions is important, and PDT guarantees good cosmetic results in many of the cases where BD is located in the lower extremities (usually in older women) [12]. In these cases, PDT is the most commonly used treatment instead of curettage and cryotherapy, curettage and electrodessication or topical 5-fluorouracil cream (the treatment modalities most commonly used in BD lesions on the trunk and upper extremities). Nevertheless, in the study carried out by Truchuelo et al it was found that BD lesions in the lower extremities treated with PDT had worst outcome [10]. The results of the present work show a response in the lower extremities similar to that obtained in other locations unlike the Truchuelo study.

Although no local anesthesia is needed, it is very common for patients to experience some pain or discomfort during PDT treatment, typically described as a burning or prickling sensation. Discomfort is greater when treating large areas on the face, scalp and hands, albeit the demonstrated ability of PDT to provide superior cosmetic outcome to standard therapy and more rapid healing could make this treatment recommendable. The use of cool air or sprayed cold water can help relieve pain [16]. However, use of topical anesthesia has been discouraged for interfering with the MAL/ALA absorption [29]. Recently, in the search for more effective protocols, some researchers have investigated the pre-treating of the lesions with fractional ablative lasers (CO_2, Er:YAG) assisted MAL/PDT, which has resulted in an improvement of both CRR and RR [22,23]. In these cases application of anesthesia is needed as well as the management and maintenance of more light systems, which complicates and makes the process more expensive. Adverse reactions as scarring, hyper or hypopigmentation following topical MAL/PDT are uncommon after MAL/PDT in BD treatment; however, some cases of erythema have been reported after MAL/PDT intervention [13,15]. In our study, some patients showed mild hypopigmentation that improved over time. In general, PDT is associated with minimal adverse reactions for BD treatment [24].

There are some studies comparing MAL/PDT with other methods in the treatment of BD. Morton et al [25] compared the efficacy of MAL/PDT vs cryotherapy and 5-Fu in the treatment of BD in the short and long term. They concluded that PDT showed superiority as for cosmetic outcome, CRR and RR even at 12 months. In a retrospective study of 263 lesions [30], RR was evaluated for 8 years of follow-up after application of surgical excision, cryotherapy and MAL/PDT. Although RR was 0.8%, 4.7% and 18% respectively, authors observed that less invasive methods may sometimes be preferred, as for example PDT for BD of the lower extremities [30]. At the present time, the trend is to consider that no treatment modality is clearly superior. Location, size, thickness and number of lesions are the main factors to take into account to choose one treatment over another. The patient´s characteristics, clinician´s expertise, availability of therapy, and the institutional experience are also important in selection of the therapeutic approach [30]. Finally, the introduction of new, non-invasive therapies for NMSC has to be analyzed in terms of their efficacy but also from a cost perspective. Aguilar et al, evaluating the cost of MAL/PDT, imiquimod and conventional surgery for BD treatment of the lower extremities found that conventional surgery average cost was greater than that of MAL/PDT or imiquimod, at least after the first 2 years of follow-up [31]. PDT is confirmed to be an economic procedure and no large infrastructure is needed in the private practice.

Results of the present work confirm that PDT applied in 3 sessions spaced 4 weeks, using red light (˜ 630 nm) at 75 J/cm^2 following application of MAL under occlusion for 3 h, allows to obtain optimal clearance rates for the treatment of BD and very good cosmetic outcomes with scarce side effects.

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