Original Article


Introduction

Bowen’s disease (BD) or squamous cell carcinoma in-situ is a form of intraepidermal carcinoma which may ultimately progress to an invasive squamous cell carcinoma. Most studies have suggested a 3-5% risk of progression to invasive SCC. Traditional treatments for BD include 5-fluorouracil (5-FU), topical imiquimod, cryotherapy, curettage, excision, radiotherapy and more recently topical photodynamic therapy...
PDT involves the activation of a photosensitizer, usually a porphyrin derivative by irradiation from an appropriate light source. Topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) are the most commonly used topical photosensitizers. Previous studies have reported clearance rates of 86-93% after treatment with PDT. However, most of these published data have been on Fitzpatrick skin type I/II patients. There are currently no studies looking at the effectiveness of PDT on patients with Fitzpatrick skin type III/IV in the literature. We present our findings on the effectiveness of MAL-PDT in the treatment of BD in a cohort of Chinese patients seen at the National Skin Centre, Singapore from 2006 to 2010.

Materials and methods

Patients
A retrospective analysis of Chinese patients (Fitzpatrick Skin Type IV) with biopsy-proven BD seen at the National Skin Center from March 2006 to March 2010 was carried out. A total of 43 patients with 56 cases of histologically confirmed BD were recruited. The study was approved by the country’s ethics committee.

Treatment protocol
Prior to each treatment session, the lesions were prepared by removing the overlying crust and scaling with a curette. A 1-mm thick layer of methyl-aminolevulinate (MAL) cream (Metvix™ 160 mg/g; Photocure ASA, Hoffsvieien 48, NO-0377, Oslo, Norway) was then applied to each lesion with a 5-mm margin surrounding the lesion. Each lesion was subsequently covered with an occlusive dressing (Tegaderm™ and 3M Micropore™; Beidersdorf AS, Birkeroed, Denmark) for 3 hours. The dressings were removed after 3 hours and the cream washed off with 0.9% saline solution before illumination with red light using a light-emitting diode lamp (Aktilite™ CL128, Photocure ASA, Hoffsvieien 48, NO-0377, Oslo, Norway) at 570-670 nm (peak wavelength at 630 nm). The illumination time was 8 min 12 s, with a total dose of 37 J/cm² at 5-8 cm lamp-skin distance, with a lamp irradiance of 75 mW/cm². During illumination, the patient wore protective eyewear.

The majority of lesions received two sessions of PDT, three lesions received one session of PDT and one lesion received three sessions of PDT. Forty-two lesions were treated one week apart, 7 lesions two weeks apart, one lesion three weeks apart and two lesions four weeks apart.

Data analysis
Clinical pictures were taken before treatment and one month after the second session of PDT. Patients were followed up at 1 month, 3, 6 and 12 months after last PDT session. The clinical response at 1, 3, 6 and 12 months were evaluated by the same two clinicians. Patients were asked to evaluate the intensity of pain experienced during and after PDT using a visual analogue pain scale (VAS). The scores ranged from 0 to 10 where 0 represented no pain and 10 the highest pain level. Any local or systemic adverse events were carefully recorded during the treatment and subsequently at each follow-up visit.

Incomplete or recurrent lesions were treated with further two PDT treatment sessions, liquid nitrogen cryotherapy, 5-FU, topical imiquimod or excised surgically.

Results

Baseline clinical characteristics
A total of 43 Chinese patients, 16 females and 27 males with ages ranging from 33 to 96 years (mean age of 71.4 years) diagnosed with biopsy-proven Bowen’s disease were treated with MAL-
PDT treatment at the National Skin Centre, Singapore from March 2006 to March 2010. All patients were of Fitzpatrick skin phototype IV.

A total of 56 lesions with a mean diameter of 23 mm (5-35 mm) were treated. The majority of patients had one lesion followed by patients with two or more lesions. The most commonly affected anatomical location was the head and neck region 19/56 (33.93%). This was followed by upper limbs 16/56 (28.57%), trunk 11/56 (19.64%) and finally the lower limbs and genitalia with 5/56 (8.93%) lesions each (Table 1).

Greatest diameters ranged from 5 to 14 mm in 8 lesions, from 15 to 29 mm in 21 lesions and were greater than 30 mm in 19 lesions. The diameters were not recorded in 8 lesions. Fifty-two lesions received two sessions of PDT, three lesions received one session of PDT and one lesion received three sessions of PDT.

The treatment intervals was one week for 42 of the lesions, two weeks for 7 of the lesions, three weeks for one lesion and four weeks for two lesions. Treatment intervals were not recorded in four lesions. The mean duration of follow-up was 25.1 months.

**Response rates at 3, 6 and 12 months**

The overall clearance rate was 73.2% (41/56) at three months. The clearance rate at three months for lesions with diameters between 5 to 14 mm was 87.5%, 71.4% for lesions with diameters between 15 to 29 mm and 78.9% for lesions with diameters greater than 30 mm (Table 2). Eleven lesions were persistent and four lesions were recurrent at three months post-PDT. Three of the recurrent lesions were localized to the base of penis and scrotum, while one was localized to the arm.

Amongst the 11 persistent lesions present in 8 patients, two were renal transplant patients on immunosuppressants, one patient had epidermodysplasia verruciformis. Excluding the total number of lesions in immunosuppressed patients and in patients with immunogenetic defects, the clearance rate at three months was 80.3%. The clearance rate was 85.7% for lesions treated twice one week apart at three months (Figure 1).

Two patients defaulted at the 6 months follow-up. There were four recurrences and one patient showed progression of BD to invasive SCC after 6 months. Of the recurrences, two were localized to the lower limbs, one on the glans penis and one on the upper eyebrow. The clearance rate at 6 months was 73.5% (36/49).

**Table 1. Baseline characteristics of the patients**

<table>
<thead>
<tr>
<th>Number of patients:</th>
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<tbody>
<tr>
<td>Total</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>71.4 (33-96)</td>
</tr>
<tr>
<td>Fitzpatrick skin type III/IV</td>
<td>43</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>56</td>
</tr>
<tr>
<td>Locations of lesions:</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>19 (33.93%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>11 (19.64%)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>16 (28.57%)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>5 (8.93%)</td>
</tr>
<tr>
<td>Genitalia</td>
<td>5 (8.93%)</td>
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</tbody>
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**Table 2. Clearance by size of lesion**

<table>
<thead>
<tr>
<th>Size of lesions (mm)</th>
<th>No. of lesions (n=48)</th>
<th>Clearance at 3 months, n (%)</th>
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<tbody>
<tr>
<td>5-14</td>
<td>8</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>15-29</td>
<td>21</td>
<td>15 (71.4%)</td>
</tr>
<tr>
<td>≥30</td>
<td>19</td>
<td>15 (78.9%)</td>
</tr>
</tbody>
</table>

*Size data on 8 lesions absent*
Follow-up data at 12 months was available for the 37 lesions that had cleared at three months post-PDT. There were recurrences in 8 of the 37 lesions (21.6%) at 12 months follow-up.

**Safety and tolerability**
The main side-effects experienced include mild to moderate degrees of erythema, pain and oedema during light application. Pain was the most common side effect and 74.4% (32/43) of patients experienced some degree of pain during treatment. Nine patients had a VAS score of 0, 15 patients had a VAS score of 1-3, 12 patients had a VAS score of 4-7, 4 patients had a VAS score of 8-10. Pain score was not stated in 2 patients and 1 patient had dementia. Two patients developed bleeding and five developed oozing and crusting following treatment. All patients developed transient post-inflammatory hyperpigmentation post-PDT treatment which resolved by 6 months. Other local and systemic adverse events related to the treatment were not found.

**Discussion**
There is currently no gold standard treatment modality for Bowen’s disease. All treatments have advantages and disadvantages and the clinician’s decision is often dependent on lesional factors (e.g. size, site, number, potential for healing or functional impairment). The British guidelines for management of Bowen’s disease published in 2006 listed evidence for various treatment options available such as topical 5-FU, topical imiquimod, cryotherapy, curettage, excision, radiotherapy, laser, and topical PDT with either ALA or MAL photosensitizer which has gained popularity in the last ten years.2

Much of the earlier published studies using topical ALA-PDT showed that ALA-PDT cleared, on average, 86-93% of BD lesions following one or two treatments.3,4 The published clinical clearance rates for MAL-PDT are 73-87.8% after 3 months.5,6 Multiple studies have demonstrated the efficacy of topical PDT for treatment of BD being equivalent
or superior to both cryotherapy and topical 5-FU.\textsuperscript{1,4,6-8} Topical PDT also gave superior cosmetic results when compared to cryotherapy or 5-FU.\textsuperscript{1,6}

The British guidelines currently recommend PDT therapy (with ALA or MAL photosensitizer) with a strength of recommendation A and quality of evidence I for treatment of BD.\textsuperscript{1} It is particularly advantageous for large multiple lesions and for lesions located at poor healing sites.\textsuperscript{1} The benefits of topical PDT are that it is a good alternative at surgically difficult sites, heals rapidly, has good cosmesis and fewer side-effects compared to surgical excision, topical 5-FU and cryotherapy.\textsuperscript{3,7,8}

All published data on topical PDT however have been on Fitzpatrick skin types I/II. To our knowledge, that this is the first retrospective study looking at topical PDT in the treatment of BD in patients with Fitzpatrick skin phototype IV.

In our study, the overall clearance rate at 3 months was 73.2%. Excluding patients on immunosuppressives and immunogenetic defects, the clearance rate at 3 months increased to 80.3%. The clearance rate decreased to 73.5% at 6 months follow-up. The worst clinical response was detected in the genitalia region with only one out of five scrotal/penile lesions obtaining complete clearance after 6 months. This is in agreement with previous studies and reports which found MAL-PDT to be only partially effective in treating erythroplasia of Queyrat (EQ) lesions with high recurrence rates.\textsuperscript{9,10} Most studies caution the use of PDT in EQ lesions as a first-line therapeutic option.\textsuperscript{9,10}

Recently, both Evangelou et al and Matthews et al showed that in addition to the immune stimulating effects of PDT, PDT can lead to immunosuppression. Evangelou et al biopsied buttock skin treated with ALA-PDT and found a significant reduction in epidermal Langerhans cells after PDT.\textsuperscript{12,16} Langerhans cells are important antigen-presenting cells in the skin with a major role in the recognition of foreign antigens and their presentation to T lymphocytes. Their reduction could thus negatively impact on antitumor responses. Matthews et al demonstrated significant immune suppression in healthy volunteers treated with standard dose high-irradiance topical PDT, using Mantoux reactions to determine immunosuppression. MAL-PDT and ALA-PDT were found to significantly suppress Mantoux erythema and diameter.\textsuperscript{16} Both groups concluded that topical PDT induced significant immune suppression which could impair local antitumour immune responses and thus contribute to treatment failure. PDT-induced immunosuppression in our inherently immunosuppressed patients may explain the
presence of persistent lesions and recurrences in our study resulting in a lower overall clearance rate.

Frost et al also demonstrated that PDT immunosuppression was influenced by the fluence rate. In the study, PDT caused significant, dose-response immunosuppression at high (75 mW/cm²) fluence rate but not at lower (15 or 45 mW/cm²) fluence rates. DNA photolesions, triggers for immunosuppression, were also observed in high-fluence-rate PDT but not lower fluence-rate PDT. The study suggested that the standard current PDT protocol which utilizes 75 mW/cm² is immunosuppressive. Reducing the irradiation rate while maintaining other parameters may have the potential to improve clearance rates.

Another possible explanation for the overall lower than reported clearance rate is the photo-protective property of melanin. All our patients had Fitzpatrick type IV skin type. Melanin absorbs light over the wavelength used for PDT (630 nm) which results in inadequate penetration of light into the tumour base. Melanin also has the ability to markedly reduce singlet oxygen yields and scavenge free radical species. Radical scavenging limits the efficacy of ionizing radiation. Eumelanin absorbs light between 300 and 1000 nm. At 630 nm, it absorbs 10-15%. The manufacturer of Aktilite™ suggested increasing the dose of red light from 37 J/cm² to 41-43 J/cm² to compensate for melanin absorption.

PDT is generally well tolerated. The main adverse event associated with PDT is pain. It is typically a burning or stinging sensation during illumination which usually resolves within hours but can rarely persist up to several days. Pain relief for majority of patients involves cooling the illumination site with cold water. Local anaesthesia can be reserved for patients experiencing severe pain.

There are several limitations to our study in that it was a retrospective analysis with small patient numbers. In addition, a number of patients were lost to follow-up after 12 months. The treatment regimen was non-standardized with several lesions treated more than one week apart.

In conclusion, we present our study demonstrating the efficacy of topical PDT (MAL-PDT) in BD in a cohort of Fitzpatrick skin phototype IV individuals. While PDT remains a useful treatment modality for BD and is generally well-tolerated, the clearance rate is lower in racially pigmented individuals. We propose increasing the dosage of the red light by 10-15% to 41-43 J/cm² to overcome increased melanin absorption. Treatment can also be optimised to two cycles of treatment with the first cycle of two treatments one week apart separated from the second cycle of treatment by a period of three months. There is currently no data available in the literature on the optimal dosimetry regime for PDT in Asian skin. Our study may be the first to suggest an alternative dosimetry regime for this group of patients.

References


