*Hong Kong J. Dermatol. Venereol.* (2012) **20**, 53-59

Original Article

# A study of topical methyl-aminolevulinate red-light photodynamic therapy in the treatment of squamous cell carcinoma-in-situ in Chinese patients: a Singaporean experience

# 新加坡的光動力療法經驗：一項對鱗狀上皮細胞原位癌的華裔患者使用外用甲基氨基乙酰丙酸紅光光動力療法的研究

CSL Koh 高淑玲, HY Chia 謝慧儀, C Theng 唐添成, WS Chong 張維盛

Topical photodynamic therapy is used in the treatment of Bowen's disease (BD). This is a retrospective review of the data of Chinese patients with BD who have undergone photodynamic therapy at the National Skin Centre from March 2006 to March 2010. A total of 43 Chinese patients with 56 histologically confirmed BD were included. The clearance rate at 3 months was 73.2%. Pain was the most common side effect. The clearance rate in our patients is lower than rates cited in current literature. Future prospective studies utilizing topical PDT in the treatment of BD in Asian skin are needed to evaluate its efficacy in Asian patients.

外敷光動力療法是鮑恩氏病的其中一種治療方法。本研究回顧分析了新加坡國家皮膚病中心，自二零零六年三月至二零一零年三月間，對華裔鮑恩氏病患者所施行的光動力治療。當中包括四十三名華裔病患，計有五十六個組織學確立的鮑恩氏病病灶。三個月的清除率爲百分之七十三點二；疼痛是最常見的副作用。 我們病患的清除率相對當前文獻記載爲低，故需要進一步的前瞻性研究去釐清外敷光動力療法對亞洲人膚色的鮑恩氏病之成效。

**Keywords:** Asian, Bowen's disease, Fitzpatrick skin phototype IV, Photodynamic therapy

**關鍵詞**：亞洲人，鮑恩氏病，第五型曝光反應的膚質類型，光動力療法

**Department of Dermatology, Liverpool Hospital, Sydney, Australia**
CSL Koh, MBBS, DPD(Cardiff)

**National Skin Center, Singapore**
CSL Koh, MBBS, DPD(Cardiff)
HY Chia, MBBS, MRCP(UK)
C Theng, MRCP(UK), FAMS(Dermatology)
WS Chong, MRCP(UK), FAMS(Dermatology)

Correspondence to: Dr. CSL Koh

Skin and Cancer Foundation, Darlinghurst, 277 Bourke Street, Darlinghurst NSW 2010, Australia

## Introduction

Bowen's disease (BD) or squamous cell carcinoma (SCC) 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.[1] Traditional treatments for BD include 5-fluorouracil (5-FU), topical imiquimod, cryotherapy, curettage, excision, radiotherapy and more recently topical photodynamic therapy

(PDT).[2] PDT is a well-established therapeutic option that has been approved for treatment of BD in many countries.

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.[3] 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, Hoffsveien 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, Hoffsveien 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/cm$^2$ at 5-8 cm lamp-skin distance, with a lamp irradiance of 75 mW/cm$^2$. 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 was on immunosuppressants for systemic lupus erythematosus (SLE) and 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).

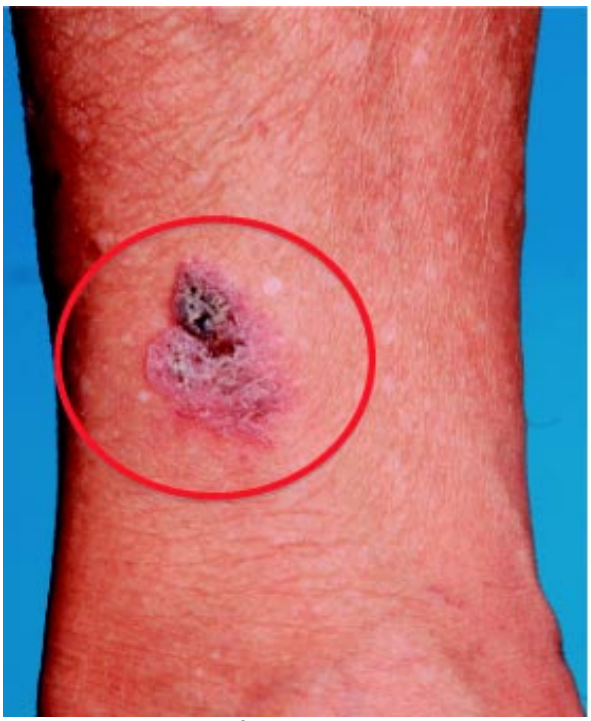
**Table 1.** Baseline characteristics of the patients

| | |
|---|---|
| Number of patients: | |
| Total | 43 |
| Male | 16 |
| Female | 27 |
| Mean age, years (range) | 71.4 (33-96) |
| Fitzpatrick skin type III/IV | 43 |
| Number of lesions | 56 |
| Locations of lesions: | |
| Head and neck | 19 (33.93%) |
| Trunk | 11 (19.64%) |
| Upper limbs | 16 (28.57%) |
| Lower limbs | 5 (8.93%) |
| Genitalia | 5 (8.93%) |

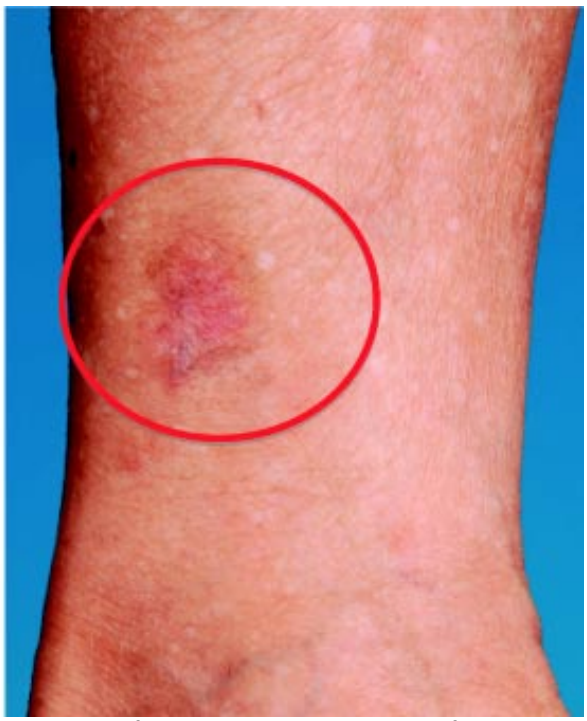
**Table 2.** Clearance by size of lesion

| Size of lesions (mm) | No. of lesions (n=48) | Clearance at 3 months, n (%) |
|---|---|---|
| 5-14 | 8 | 7 (87.5%) |
| 15-29 | 21 | 15 (71.4%) |
| ≥30 | 19 | 15 (78.9%) |

*Size data on 8 lesions absent



Bowen's disease on left leg prior to PDT



Clearance of Bowen's disease 3 months after PDT

**Figure 1.** Bowen's disease before and after PDT.

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.[1,4,6-8] Topical PDT also gave superior cosmetic results when compared to cryotherapy or 5-FU.[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.[1] It is particularly advantageous for large multiple lesions and for lesions located at poor healing sites.[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.[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.[9,10] Most studies caution the use of PDT in EQ lesions as a first-line therapeutic option.[9,10]

There was also a lower overall clearance rate with larger BD lesions. In our study, the clearance rate for BD lesions between 5 to 14 mm in diameter was higher than those between 15 to 29 mm and lesions 30 mm or larger (87.5% vs 71.4% vs 78.9%). Morton et al compared the complete response rates between topical MAL-PDT with cryotherapy and topical fluorouracil for treatment of BD lesions and found that the maximum lesion diameter had a statistically significant influence on the complete response rate in all treatment groups with larger lesion diameters having lower response rates ($p<0.001$).[6] Morton also concluded that larger patches of BD may require more than two PDT treatments to obtain complete clearance.[11]

There is evidence that PDT elicits both immune-stimulating as well as immunosuppressive responses.[12,13] Studies have shown that during the acute phase of the response to PDT, pro-inflammatory mediators are released, attracting circulating polymorphs and mononuclear cells to the treated site as well as upregulation of adhesion molecules.[12,14] The mechanisms by which PDT-induced immunostimulatory responses destroy tumour cells include generating reactive oxygen species, by infiltrating neutrophils and altering expression of cellular responses to various immunomodulatory cytokines.[13,15]

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.[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.[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.[17] In the study, PDT caused significant, dose-response immunosuppression at high (75 mW/cm$^2$) fluence rate but not at lower (15 or 45 mW/cm$^2$) 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/cm$^2$ 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 Fiztpatrick 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.[18] Melanin also has the ability to markedly reduce singlet oxygen yields and scavenge free radical species.[19] Radical scavenging limits the efficacy of ionizing radiation.[20] 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/cm$^2$ to 41-43 J/cm$^2$ 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/cm$^2$ 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


1. Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowen's disease. Br J Dermatol 1999; 141:633-41.
2. Cox NH, Eedy DJ, Morton CA; Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists. Guidelines for management of Bowen's disease: 2006 update. Br J Dermatol 2007;156:11-21.
3. Morton CA, Brown SB, Collins S, Ibbotson S, Jenkinson H, Kurwa H, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002;146: 552-67.
4. Morton CA, McKenna KE, Rhodes LE; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. Br J Dermatol 2008;159:1245-66.
5. Calzavara-Pinton PG, Venturini M, Sala R, Capezzera R, Parrinello G, Specchia C, et al. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. Br J Dermatol 2008;159: 137-44.
6. Morton C, Horn M, Leman J, Tack B, Bedane C, Tjioe M, et al. Comparison of topical methyl aminoleuvulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results

of a multicenter randomized trial. Arch Dermatol 2006; 142:729-35.
7. Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol 2003;148:539-43.
8. Morton CA, Whitehurst C, Moseley H, McColl JH, Moore JV, Mackie RM. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. Br J Dermtol 1996;135:766-71.
9. Varma S, Holt PJ, Anstey AV. Erythroplasia of Queyrat treated by topical aminolaevulinic acid photodynamic therapy: a cautionary tale. Br J Dermatol 2000;142: 825-6.
10. Stables GI, Stringer MR, Robinson DJ, Ash DV. Erythroplasia of Queyrat treated by topical aminolaevulinic acid photodynamic therapy. Br J Dermatol 1999;140:514-7.
11. Morton CA, Whitehurst C, McColl JH, Moore JV, MacKie RM. Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. Arch Dermatol 2001;137:319-24.
12. Evangelou G, Farrar MD, White RD, Sorefan NB, Wright KP, McLean K, et al. Topical aminolaevulinic acid-photodynamic therapy produces an inflammatory infiltrate but reduces Langerhans cells in healthy human skin *in vivo*. Br J Dermatol 2011;165:513-9.
13. Wong TW, Tracey E, Oseroff AR, Baumann H. Photodynamic therapy mediates immediate loss of cellular responsiveness to cytokines and growth factors. Cancer Res 2003;63:3812-8.
14. Cecic I, Parkins CS, Korbelik M. Induction ofsystemic neutrophil response in mice by photodynamic therapy of solid tumors. Photochem Photobiol 2001;74:712-20.
15. Gollnick SO, Musser DA, Oseroff AR, Vaughan L, Owczarczak B, Henderson BW. IL-10 does not play a role in cutaneous Photofrin photodynamic therapy-induced suppression of the contact hypersensitivity response. Photochem Photobiol 2001;74:811-6.
16. Matthews YJ, Damian DL. Topical photodynamic therapy is immunosuppressive in humans. Br J Dermatol 2010; 162:637-41.
17. Frost GA, Halliday GM, Damain DL. Photodynamic therapy-induced immuosuppression in humans is prevented by reducing the rate of light delivery. J Invest Dermatol 2011;131:962-8.
18. Pass HI. Photodynamic therapy in oncology: mechanisms and clinical use. J Natl Cancer Inst 1993; 85:443-56.
19. Hadjur C, Richard MJ, Parat MO, Jardon P, Favier A. Photodynamic effects of hypericin on lipid peroxidation and antioxidant status in melanoma cells. Photochem Photobiol 1996;64:375-81.
20. Slominski A, Paus R, Mihm MC. Inhibition of melanogenesis as an adjuvant strategy in the treatment of melanotic melanomas: selective review and hypothesis. Anticancer Res 1998,18:3709-15.