Photodynamic Therapy for Large or Multiple Patches of Bowen Disease and Basal Cell Carcinoma

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Background: Photodynamic therapy (PDT) using topical δ-aminolevulinic acid (δ-ALA) is an effective treatment for Bowen disease and certain basal cell carcinomas (BCCs), but its place in clinical practice remains to be established. Patients with large and/or multiple lesions of Bowen disease or BCC can represent a considerable therapeutic challenge. We suggest that δ-ALA PDT may be of particular benefit in such patients.

Observation: In an open study, 35 (88%) of 40 large patches of Bowen disease, all with a maximum diameter greater than 20 mm, cleared following 1 to 3 treatments of δ-ALA PDT, although 4 patches recurred within 12 months. δ-Aminolevulinic acid PDT was also used to treat 40 large BCCs, with an identical 88% initial clearance (after 1-3 treatments), with 4 recurrences within 34 months (range, 12-60 months). In 10 further patients with multiple (≥3) patches of Bowen disease, 44 (98%) of 45 patches cleared following δ-ALA PDT, although 4 lesions recurred over 12 months. In 3 patients with multiple BCCs, PDT cleared 52 (90%) of 58 lesions, with 2 recurrences during 41 months (range, 12-52 months). Treatments were well tolerated, with only 5 patients with solitary large lesions requiring local anesthesia.

Conclusions: δ-Aminolevulinic acid PDT is an effective tissue-sparing modality achieving good cosmesis. We propose that δ-ALA PDT be considered as a first-line therapy for large and/or multiple areas of Bowen disease and superficial BCCs.

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OPICAL photodynamic therapy (PDT) with δ-aminolevulinic acid (δ-ALA) in patients with Bowen disease achieves clearance rates of 90% to 100% following 1 to 3 treatments.1-6 Basal cell carcinomas (BCCs) can also clear following PDT, although tumor thickness is a predictor of clearance, with superficial lesions the most likely to respond.7

Photodynamic therapy involves the activation of a photosensitizing drug by visible light to produce activated oxygen species that promote tumor destruction. Exogenous δ-ALA increases the intracellular production of the endogenous photosensitizer protoporphyrin type IX, via the heme pathway, with preferential accumulation in neoplastic or dysplastic tissue.8

Several other modalities exist for Bowen disease9 and BCCs,10,11 although their use may be limited by practical considerations in large and/or multiple lesions. Surgery may be complicated by the requirement for grafts, poor healing, and obvious scars, while cryotherapy or topical chemotherapy may require multiple treatments and result in poorly tolerated adverse effects in the generally elderly population receiving treatment. Curettage is suboptimal for large lesions, with the recurrence rate of BCCs known to increase with tumor diameter.12 Radiotherapy can require full tumor doses in those with Bowen disease and BCCs, with the risk of failure to heal or prominent scarring.13 The option of a tissue-sparing modality with reported good cosmesis could have a place in the management of such lesions. We, therefore, assessed the potential of δ-ALA PDT in large and/or multiple lesions of patients with Bowen disease and BCC.

RESULTS

BOWEN DISEASE

Eighty-five patches of Bowen disease received treatment, with 40 large lesions greater than 20 mm in diameter and 45 multiple lesions.

The 40 large patches were situated on the face (n=3), trunk (n=8), upper limbs (n=4), or lower limbs (n=25). While 2 patients had 2 lesions, the remaining 36 had...
PATIENTS, MATERIALS, AND METHODS

Ethical committee approval was obtained for the treatment of patients with Bowen disease and BCC by PDT. Sequential patients with biopsy-proven disease were invited to participate. In patients with multiple lesions, representative biopsies were performed. No lesion had been previously treated. Patients with nevoid BCC syndrome were excluded to focus this study on the response of typical superficial BCC to 5-ALA PDT.

The patented lamp used (Paterson PDT lamp; Photo Therapeutics Ltd, Manchester, England) incorporates a 300-W xenon short arc plasma discharge. The spectral output of the lamp was filtered to 630±15 nm, with the field of illumination varied between 4 and 8 cm in diameter depending on lesion size, permitting at least a 5-mm margin around the tumor margin. The illumination time for 100 J/cm² and a 4 × 4 cm diameter field was 40 minutes, with longer exposure times for the same dose to larger fields—up to 92 minutes for an 8-cm field. Topical 5-ALA in an oil in water emulsion (20% wt/wt) (Sigma Chemical Co, Poole, England; and Crawford Pharmaceuticals, Milton Keynes, England) in Unguentum Merck (E. Merck Ltd, West Drayton, England) was applied to lesions 4 or 6 hours preillumination for Bowen disease and BCC, respectively. Surface crusts were removed, and the surface was gently abraded before 5-ALA application. Approximately 50 mg/cm² of cream was applied to cover a 2 × 2 cm² lesion and a 5-mm clinically disease-free margin. The cream was kept in place under an occlusive dressing (Tegaderm; 3M, Loughborough, England) and screened from light. The patient was offered local anesthetic (1% plain lidocaine by intradermal injection) during treatment.

The enrollment criteria, dosage, and treatment schedules for each part of the study are summarized in Table 1. The division of lesions into groups dependent on a largest diameter of 20 mm or smaller was arbitrary, but chosen on the hypothesis that lesions larger than 20 mm in diameter in practice represent a greater management challenge to direct excision and closure or to cryotherapy to the entire field on a single visit. Clinical response was determined after 6 weeks, and subsequent treatments were administered if lesions did not appear to have completely cleared.

Following the clinical determination of clearance, all patients were observed at 2-month intervals for 12 months to look for recurrence, and the patients with BCCs were maintained under long-term observation. Posttherapy punch biopsies were performed in all single BCC lesions, in representative lesions in patients with multiple BCCs and Bowen disease, and in patients in whom doubt about clinical clearance or recurrence existed.

Surface fluorescence was detected by a UV lamp (UV56 lamp; UVP, Upland, Calif), with peak emission at 365 nm. The presence of fluorescence was recorded before illumination of all treatment sites and on the completion of each treatment session. Fluorescence was estimated, by the same investigator (C.A.M.), using an arbitrary scale: 0 indicates not detectable; 1, just visible; 2, moderate; 3, strong; and 4, very intense.

Patients scored pain during and following treatment on a 10-cm visual analog scale (with subsequent interpretation of 0 < x ≤ 3 as mild, 3 < x ≤ 7 as moderate, and 7 < x ≤ 10 as severe).

Formal statistical methods were considered for analyzing the patterns of clearance (cleared after 1, 2, or 3 treatments or not cleared), allowing for possible effects of lesion size (Bowen disease and BCC) and thickness (BCC only). Two types of logistic regression models for multigroup responses were considered: nominal–response models, in which the slopes of the logistic functions for the various categories are not constrained to be parallel; and proportional-odds models, in which the slopes are constrained to be parallel. In some cases, the data were too sparse to allow these models to be fitted satisfactorily, either due to small numbers of subjects or small numbers of events (eg, nonclearance).

For the Bowen disease data, multigroup logistic models were fitted, where the explanatory variable was the logarithm of lesion size. A proportional-odds model was found to give a satisfactory fit to the data. For the BCC data, multigroup logistic models were also fitted for the subject with 42 lesions treated. Clearly, this model is not generalizable to other individuals but does give a unique insight into the clearance of BCC for this one individual. A proportional-odds model did not fit the data adequately, but a more complicated nominal–response model did. In this model, the response categories of clear after 1 or 2 treatments were modeled relative to the reference category of not cleared.

1 large lesion. The mean age of patients was 76 years (range, 44-93 years), with 29 women and 9 men. Thirty-five lesions (88%) cleared (Figure 1) after 1 to 3 treatments (Table 2). Five patches failed to clear during 3 treatments, although all showed a partial response. Surface fluorescence at grade 3 or 4 was present in all lesions, although all showed a partial response. Surface fluorescence at grade 3 or 4 was present in all lesions, although all showed a partial response. Surface fluorescence at grade 3 or 4 was present in all lesions, although all showed a partial response. Surface fluorescence at grade 3 or 4 was present in all lesions, although all showed a partial response.

Following the 12-month follow-up, 4 lesions recurred, reducing overall clearance to 78%.

Ten further patients, all women (mean age, 70 years; age range, 52-83 years), had 45 patches of Bowen disease situated on the lower legs (n = 42) or hands (n = 3). Four patients had 3 lesions, 3 had 4 lesions, and 1 each had 5, 7, and 9 patches. Forty-four lesions cleared following 1 or 2 treatments (Table 2), to achieve an initial complete response rate of 98%. There was no significant difference in average size between those lesions requiring 1 and 2 treatments. During follow-up, 4 lesions recurred, reducing the clearance rate after 12 months to 89%.

Site did not have any effect on clearance, with clearance of 63 (94%) of 67 leg lesions, 7 of 8 trunk lesions, 6 of 7 upper limb lesions, and all 3 facial patches.

BASEAL CELL CARCINOMA

Eighteen patients (11 men and 7 women; mean age, 65 years; age range, 45-81 years) with 73 large and/or multiple BCCs underwent 5-ALA PDT. Fifteen patients had solitary large lesions and 1 each had 4 (patient 1), 12 (pa-
tient 2), and 42 (patient 3) BCCs. Surface fluorescence at grade 3 or 4 was present in all lesions before therapy and absent on completion of illumination.

Clearance rates are shown in Table 2, with 35 (88%) of 40 large lesions initially clearing (14 of 15 solitary BCCs and 21 of 25 large lesions from patient 3). Figure 2 demonstrates the response of one of the large superficial lesions to δ-ALA PDT.

In patients 1 and 2, the representative biopsies indicated superficial disease that extended no deeper than 0.3 mm. All 16 lesions cleared following 1 (n=14) or 2 (n=2) treatments, with no recurrences for 40 and 41 months, respectively.

Patient 3, with 42 lesions at presentation (Figure 3A), underwent radiotherapy for acne at the age of 22 years and began developing BCCs 20 years later. After many surgical excisions, he was referred for consideration of alternative therapies. Of 42 lesions, 25 were greater than 20 mm in diameter. He had 20 biopsies performed to establish tumor thickness as accurately as possible. Lesions for which a biopsy was not performed appeared clinically similar to anatomically adjacent BCCs, in which the tumor thickness was already known. Initial clearance of 36 of the 42 lesions (Figure 3B) was achieved. For those lesions not clearing, 1 large solitary lesion cleared following a fourth application and the remaining 4 partially cleared, with reepithelialization observed.

The mean tumor thickness for the 42 lesions in patient 3 was 0.8 mm (range, 0.3-1.8 mm); for the 15 large solitary BCCs, it was 0.7 mm (range, 0.3-1.8 mm). In the logistic regression models comparing the categories “clear after 1 treatment” and “clear after 2 treatments” with “not clear,” lesion thickness (P = .004 and P = .01, respectively), but not largest diameter (P = .31 and P = .94), was found to have a significant effect on clearance for the 42 lesions of patient 3. Comparison of tumor size, with response for all 73 treated lesions, is shown in Table 3, but summary statistics were not performed because of the small number of single lesions treated. Four recurrences, evenly spread between the different size categories, occurred after 6, 12, 16, and 36 months, including 2 lesions in patient 3. There was no observed difference in response by site, with clearance of 54 of 61 trunk lesions, 10 of 10 leg lesions, and 2 of 2 arm BCCs. By chance, no facial lesions were included, with facial lesions examined during recruitment small and solitary.

### ADVERSE REACTIONS

Treatments overall were well tolerated, with initial edema and erythema around the lesion on completion of illumination, but subsiding in 24 hours. Ulceration and infection of treated sites were not observed. Eschars formed over lesions, separating after 4 to 6 weeks. No photosensitivity reactions were observed following therapy.

During the treatment of patients with large patches of Bowen disease, pain was absent in 14 lesions, mild in 12, moderate in 6, and severe in 8, although local anesthesia was requested only for 3 larger lesions (460, 875, and 3850 mm²). Following PDT, pain persisted in the same 8 patients until day 2 in 3, day 7 in 3, and up to day 10 in the remaining 2. A similar pain profile was reported during the treatment of BCCs, with severe pain requiring lo-

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**Table 1. Enrollment Criteria and Treatment Variables**

<table>
<thead>
<tr>
<th>Group</th>
<th>Tumor Features, mm</th>
<th>Time δ-ALA Applied, h</th>
<th>Light Dose, J/cm²</th>
<th>Irradiance, mW/cm²†</th>
<th>Maximum No. of Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowen disease lesions</td>
<td>Large &gt;20, NA</td>
<td>4</td>
<td>125</td>
<td>48 (20-86)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Multiple ‡ ≤20, NA</td>
<td>4</td>
<td>125</td>
<td>86</td>
<td>2</td>
</tr>
<tr>
<td>BCCs</td>
<td>Large &gt;20, &lt;2</td>
<td>6</td>
<td>100-150</td>
<td>48 (20-86)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Multiple‡ All &lt;2</td>
<td>6</td>
<td>100-150</td>
<td>40 (20-86)</td>
<td>2 if ≤20 mm and 3 if &gt;20 mm</td>
</tr>
</tbody>
</table>

*δ-ALA indicates δ-aminolevulinic acid; BCC, basal cell carcinoma; and NA, data not applicable.
† Data are given as the median (range) where applicable.
‡There were 3 or more lesions in the same patient.
cal anesthesia in only 2 of the largest lesions (4480 and 4500 mm²). No anesthesia was requested during therapy for patients with multiple patches of Bowen disease or BCC.

We report the initial clearance of 98% of multiple small and 88% of large lesions of Bowen disease, consistent with the reported high efficacy of topical δ-ALA PDT for this condition.1-6 Of all BCCs treated in this study, 66 (90%) of 73 cleared, with 62 (85%) remaining clear during 12 to 60 months of follow-up. Published clearance rates for δ-ALA PDT in patients with BCC are generally inferior to those for patients with Bowen disease: 79% to 100% for clinically superficial lesions and 10% to 75% for nodular lesions.2-4,15-18 We previously reported the superior clearance of thin tumors by comparison of clearance rates with tumor depth measurement.7 The comparable clearance rates for large Bowen disease and BCC suggest that PDT for BCC can be as effective provided only superficial lesions less than 2 mm thick are included. We undertook a gentle abrasion of the skin surface to lift crust with the edge of a scalpel blade before δ-ALA PDT, which may improve efficacy. Soler et al19 have reported the clearance of 92% of 119 nodular BCCs 2 mm thick or greater following actual debulking curettage before δ-ALA PDT (also using dimethyl sulfoxide).

Recurrence rates for Bowen disease following δ-ALA PDT appear consistently to be 0% to 10%,1-6 an observation confirmed in this study, in which 10% of all successfully treated lesions recurred. Follow-up of treated Bowen disease for 18 to 36 months has been associated with few late recurrences.2,4 In contrast, late recurrences of BCC have been reported. Cairnuff et al2 reported an initial 88% clearance (14 of 16 lesions), but 6 (43%) of the 14 lesions recurred in 17 months (range, 4-21 months), with the median time to recurrence of 11

**COMMENT**

Table 2. Complete Response (CR) Rates Following δ-ALA PDT for Large or Multiple Bowen Disease Lesions or BCCs

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Recurrences</th>
<th>CR†</th>
<th>Overall Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowen disease lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large (n = 40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 1 Treatment</td>
<td>17 (42)</td>
<td></td>
<td>42 (88)</td>
</tr>
<tr>
<td>After 2 Treatments</td>
<td>13 (32)</td>
<td></td>
<td>32 (64)</td>
</tr>
<tr>
<td>After 3 Treatments</td>
<td>5 (12)</td>
<td></td>
<td>12 (24)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (88)</td>
<td></td>
<td>88 (176)</td>
</tr>
<tr>
<td>BCCs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large (n = 40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 1 Treatment</td>
<td>23 (58)</td>
<td></td>
<td>58 (116)</td>
</tr>
<tr>
<td>After 2 Treatments</td>
<td>11 (28)</td>
<td></td>
<td>28 (56)</td>
</tr>
<tr>
<td>After 3 Treatments</td>
<td>1 (2)</td>
<td></td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (88)</td>
<td></td>
<td>88 (176)</td>
</tr>
</tbody>
</table>

*δ-ALA indicates δ-aminolevulinic acid; PDT, photodynamic therapy; BCC, basal cell carcinoma; and NA, data not applicable.
†Data are given as the number (percentage).
‡Data are given as the mean (range).

Table 3. Response of Bowen Disease and BCC to δ-ALA PDT Depending on Lesion Size

<table>
<thead>
<tr>
<th>Lesion Size, mm²</th>
<th>Bowen Disease</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR†</td>
<td>No. of Recurrences</td>
</tr>
<tr>
<td>&lt;400</td>
<td>44/45 (98)</td>
<td>4</td>
</tr>
<tr>
<td>400-999</td>
<td>26/27 (96)</td>
<td>4</td>
</tr>
<tr>
<td>1000-1499</td>
<td>6/7 (86)</td>
<td>0</td>
</tr>
<tr>
<td>1500-1999</td>
<td>2/3 (67)</td>
<td>0</td>
</tr>
<tr>
<td>≥2000‡</td>
<td>1/3 (33)</td>
<td>0</td>
</tr>
</tbody>
</table>

*BCC indicates basal cell carcinoma; δ-ALA, δ-aminolevulinic acid; PDT, photodynamic therapy; and CR, complete response.
†Data are given as the number of CRs/total number in the group (percentage).
‡The range for the Bowen disease group was 2236 to 2930 mm²; for the BCC group, 2000 to 4500 mm².

**Figure 2.** Basal cell carcinoma: a 75 × 60-mm lesion (0.6 mm thick) before (A) and months after (B) 2 treatments with δ-aminolevulinic acid photodynamic therapy.
months. Other studies, however, show recurrence rates of only 2% to 9% after 36 months' review. We report a 6% recurrence rate (4 of 66 lesions) for BCC during 36 months of follow-up (range, 12-60 months; median, 36 months). Rowe et al reviewed the 5-year recurrence rates for BCC for different treatments: routine surgery, 10.1%; radiotherapy, 8.7%; curettage and cautery, 7.7%; cryotherapy, 7.5%; and the Mohs technique, 1.0%. This review estimates that 66% of recurrences occur by 3 years.

Available data for d-ALA PDT thus suggest that it will probably have a 5-year recurrence rate comparable to those modalities in routine clinic use.

A recent review of the management of all 68 patients with Bowen disease who presented in 1 year to a British dermatology department reported that up to 8 clinic visits (median, 4 visits) were required. In a previous study, it was noted that 20% of small lesions of Bowen disease can require 3 cryotherapy treatments to clear. This suggests that Bowen disease still represents a significant clinical management burden, with d-ALA PDT providing an effective alternative modality, clearing 76 (96%) of 79 lesions up to 4 cm in diameter in this study. Although response would appear poorer for the 3 large patches of Bowen disease, a good response for 8 (73%) of 11 BCCs greater than 4.5 cm in diameter suggests that PDT remains effective. Larger patches of Bowen disease do require more treatments, a statistical association previously observed for patches less than 21 mm in diameter, whether treated by PDT or cryotherapy. This association of lesion diameter with response has also been observed by Fritsch et al for BCC, although we have confirmed an earlier observation that, where tumor thickness is estimated by pretreatment biopsy, thickness is the primary marker of response in BCCs rather than size.

Multiple patches of Bowen disease are a common observation, recorded in 32% of patients in one retrospective study. We hypothesized that the presence of 3 or more lesions may alter a clinician's approach to treatment and hence specifically studied the outcome of d-ALA PDT in this group. Moreover, as 67 (79%) of all 85 lesions of Bowen disease were on the lower limb, for these elderly patients (mean age, 76 years), their disease posed a particular therapeutic challenge at such a poor site for healing. Although multiple BCCs are less common and were predominantly located on the trunk in our 3 patients, extensive surgery was not favored by the patients, with a tissue-sparing modality particularly sought for patient 3 by the referring plastic surgeon.

Few studies have considered the therapeutic difficulties of treating large and/or multiple lesions. In the guidelines of Albright on skin cancer therapy, large superficial lesions are classed as 14 to 20 mm in diameter, with electrosurgery recommended ahead of excision surgery and cryotherapy. Cox and Dyson observed a failure to heal 12 (20%) of 59 sites of Bowen disease on the leg following radiotherapy to lesions up to 10 cm in diameter. Stables et al cleared 3 large patches of Bowen disease by d-ALA PDT (2 treatment sessions), with clearance maintained for 12 to 26 months of follow-up. Fritsch et al reported a poorer response to PDT for BCCs greater than 4 cm, even with 3 treatment sessions, although response rates of up to 86% were achieved, depending on...
treatment variables. Fritsch et al\textsuperscript{14} also reported the efficacy of topical \(\delta\)-ALA PDT with adjunctive surgery in clearing a 10 × 6-cm superficial BCC, avoiding the need for more complex surgery.

\(\delta\)-Aminolevulinic acid PDT was well tolerated by our patients, with no ulceration or infection of treatment sites, although pain was moderate or severe in approximately one third of the patients. Pain was most likely to be severe for large lesions, and we encourage patients with particularly large lesions to have local anesthesia before illumination commences. The cosmetic outcome was generally good, although a temporary pigmentedary change with a residual faint erythematous hue and permanent localized hair loss was occasionally noted. Hair loss was particularly likely for sites of BCC treatment. Visible scars were absent, beyond biopsy sites, consistent with previous studies.\textsuperscript{1,2,5-6}

Recently published guidelines, prepared on behalf of the British Association of Dermatology, outline the management of Bowen disease\textsuperscript{9} and BCC.\textsuperscript{11} Photodynamic therapy is suggested as a good or fair choice for most presentations of Bowen disease. No treatment is recommended as first choice for large lesions of Bowen disease, although other therapies are considered to be inferior to PDT for this indication. Cryotherapy is suggested as a preferable therapy to PDT for multiple lesions in good healing sites, although our experience suggests that such multiple lesions usually occur on poor healing sites. Photodynamic therapy is considered a fair choice in superficial small and large primary BCCs in low-risk sites, but with a preference for cryosurgery or curettage.

We previously compared \(\delta\)-ALA PDT with cryotherapy in the treatment of 40 small patches of Bowen disease (including 3 patients with multiple lesions).\textsuperscript{3} Photodynamic therapy was as least as effective as cryotherapy, with fewer adverse reactions. While further comparison studies with existing modalities are required to permit refinement of the guidelines, our present study provides evidence of high clearance rates and low recurrence rates for PDT in patients with large and/or multiple Bowen disease or BCC lesions. We propose that PDT be considered as the first-line option in such lesions in which conventional therapies each have recognized limitations.

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