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GUIDELINES

Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group

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Summary Topical photodynamic therapy (PDT) is effective in the treatment of certain non-melanoma skin cancers and is under evaluation in other dermatoses. Its development has been enhanced by a low rate of adverse events and good cosmesis. 5-Aminolaevulinic acid (ALA) is the main agent used, converted within cells into the photosensitizer protoporphyrin IX, with surface illumination then triggering the photodynamic reaction. Despite the relative simplicity of the technique, accurate dosimetry in PDT is complicated by multiple variables in drug formulation, delivery and duration of application, in addition to light-specific parameters. Several non-coherent and coherent light sources are effective in PDT. Optimal disease-specific irradiance, wavelength and total dose characteristics have yet to be established, and are compounded by difficulties comparing light sources. The carcinogenic risk of ALA-PDT appears to be low. Current evidence indicates topical PDT to be effective in actinic keratoses on the face and scalp, Bowen's disease and superficial basal cell carcinomas (BCCs). PDT may prove advantageous where size, site or number of lesions limits the efficacy and/or acceptability of conventional therapies. Topical ALA-PDT alone is a relatively poor option for both nodular BCCs and squamous cell carcinomas. Experience of the modality in other skin diseases remains limited; areas where there is potential benefit include viral warts, acne, psoriasis and cutaneous T-cell lymphoma. A recent British Photodermatology Group workshop considered published evidence on topical PDT in order to establish guidelines to promote the efficacy and safety of this increasingly practised treatment modality.

Key words: 5-aminolaevulinic acid, guidelines, non-melanoma skin cancer, protoporphyrin IX, topical photodynamic therapy

Topical photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) is a potentially advantageous treatment modality (Table 1). First described by Kennedy *et al.* in 1990,[1] the proliferation of case reports and case series that followed supported the efficacy of the therapy, particularly in non-melanoma skin cancer (NMSC). However, beyond brief consideration in guidelines on

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Table 1. Advantages of topical 5-aminolaevulinic acid-photodynamic therapy

Relatively selective treatment
Minimal or no scarring
Non-invasive
Multiple lesions may be treated simultaneously
Safe
Out-patient procedure
Repeated treatments possible

treatment of Bowen's disease and basal cell carcinoma (BCC), there remains no consensus on optimal methodology or therapeutic indications.[2,3] In the U.K., 35 centres currently perform topical ALA-PDT (personal communication, Crawford Pharmaceuticals, U.K.) despite its status as an unlicensed therapy, with topical ALA available only on a named-patient basis. In November 1999, the U.S. Food and Drug Administration approved ALA-PDT (using Levulan® and the Blu-U® lamp) for the treatment of actinic keratoses.[4] In June 2001, the methyl ester of ALA (Metvix®) was approved in Sweden for topical PDT of non-hyperkeratotic actinic keratoses of the face/scalp and for BCCs unsuitable for conventional therapy (personal communication, Photocure ASA, Norway). Approvals for the rest of Europe are expected in the near future.

The increasing clinical use of topical ALA-PDT indicates a pressing need for a review of available evidence on how and when dermatologists should consider using this modality. The guidelines presented result from a British Photodermatology Group workshop held in November 2000 and are based, where available, on the data from randomized trials, and otherwise on the consensus of best practice (Appendix 1).

Drugs and method of action

The photodynamic reaction requires activation of photosensitizer in neoplastic/dysplastic tissue, by visible light and in the presence of oxygen, to produce reactive oxygen species, especially singlet oxygen, which promote tumour destruction.[5] Initially, haematoporphyrin derivatives and porfimer sodium were the photosensitizers used in cutaneous malignancy, but systemic administration and the consequent prolonged generalized photosensitivity, which can last 6–10 weeks, limited their use.[6] Systemic photosensitizers with a shorter duration of action are currently under exploration in dermatology.

Topically active agents are preferable for PDT in dermatology, and most experience to date has been with ALA. This is a precursor in the haem biosynthesis pathway, in which the endogenous photosensitizer protoporphyrin IX (PpIX) is formed, which binds with iron to form haem. Exogenous administration of ALA can increase the intracellular concentration of PpIX to therapeutically useful concentrations by bypassing a cell's feedback control, although it is metabolized within 48 h, conveniently avoiding prolonged phototoxicity. Preferential accumulation of PpIX appears to result from increased penetration of ALA through the abnormal epidermis overlying tumours, and to preferential intracellular accumulation of PpIX in proliferating, relatively iron-deficient, tumour cells.[7]

Meso-tetraphenylporphinesulphonate tetrasodium (mTPPS) and meso-tetra(hydroxyphenyl)chlorin (mTHPC) are other photosensitizers that have been applied topically, with disruption of lysosomes being central to their action.[8,9] Only single open studies of their use are described. mTPPS cleared 94% of 292 superficial BCCs with a single treatment and a 10% recurrence rate, but its development has been limited by prolonged photosensitivity and the potential for neurotoxicity.[8] mTHPC has a longer absorption maximum at 652 nm than ALA and mTPPS (both 630–635 nm) and might improve efficacy by utilizing light with deeper tissue penetration. In the sole study of its topical use, a histological clearance of only nine of 28 patches of Bowen's disease and two of seven BCCs was achieved, and formulation was considered to be a problem.[9] These agents will not be considered further in view of the limited data and current lack of evidence of any superiority over ALA-PDT.

Beyond direct tumour cell cytotoxicity, photodynamic injury to tumour vasculature probably contributes little in PDT using topically administered photosensitizers, with no direct vascular damage demonstrated by laser Doppler perfusion imaging in one study of NMSC.[10]

Drug protocols and delivery

For optimal effect, a photosensitizer should demonstrate maximum absorption at the wavelength of light used, penetrate the deeper levels and be evenly distributed throughout the lesion, and demonstrate a high lesion/normal tissue concentration ratio. The absorption peaks of PpIX are all within the visible spectrum and permit illumination by laser and non-coherent sources.[11] Fluorescence emitted by ALA-induced PpIX is an effective method of determining

the distribution of the photosensitizer and can be assessed by *in vivo* spectroscopy and fluorescence microscopy. Szeimies *et al.*[12] used fluorescence microscopy to show homogeneous fluorescence of nodular and superficial, but not morphoeic BCCs, also including tumour lobules in deep dermis, 12 h after 10% ALA application, with only skin appendages demonstrating fluorescence in specimens analysed after a 4-h application. Martin *et al.*[13] also used fluorescence microscopy to observe full-thickness fluorescence in six of seven superficial BCCs and four of nine nodular BCCs after 20% ALA application at intervals of 3–18 h. Partial-thickness fluorescence in the five remaining (and overall thicker) nodular BCCs was noted typically in the superficial part of the tumours. Roberts and Cairnduff[14] reported that PpIX distribution in BCC was most intense in those regions of tumour immediately adjacent to the dermis following application of 20% ALA for 4 h to Bowen's disease and superficial BCC. Svanberg *et al.*[7] reported a 15 : 1 tumour/normal tissue ratio of PpIX-induced fluorescence in BCC and Bowen's disease 6 h following the topical application of ALA, indicating the potential for a high degree of tumour specificity. However, much of the intense surface fluorescence was due to tumour-reactive epithelium, rather than actual tumour cells, and a ratio of 2 : 1 is more representative for tumour/dermis.

ALA is hydrophilic, but to facilitate penetration, most studies report the use of a 20% concentration in an oil-in-water emulsion. A single study using a nanocolloid lotion of ALA in treating BCC was effective, but no comparative data on different formulations exist.[15] ALA delivery through human skin can be assisted by iontophoresis, which provides an accurate means of drug dosimetry, although the usefulness of this method in clinical practice remains to be demonstrated.[16] Enhancement of ALA-PDT has been studied using the penetration enhancer dimethylsulphoxide (DMSO) and the iron chelators desferrioxamine and ethylenediamine tetraacetic acid disodium (EDTA). Only open case series of efficacy are reported in NMSC indications,[17–20] although, in a sequential three-stage study, Warloe *et al.*[21] treated BCCs using ALA alone, ALA with 2–20% DMSO + 2–4% EDTA as cofactors, or ALA and pretreatment with 50–99% DMSO. Outcomes were similar for superficial lesions, but an increase in efficacy using enhancers was observed for nodular BCC, suggesting a need for randomized comparison data. Enhanced response in ALA-PDT may also be achieved by prior debulking curettage in nodular BCC, although again no comparative data have been published.[22]

Esterified derivatives of ALA that increase its lipophilicity could potentially enhance efficacy. In non-lesional skin, equimolar concentrations of the hexyl and pentyl ester, but not butyl ester, promote higher PpIX levels and greater PpIX-induced phototoxicity than ALA.[23,24] PDT with ALA methylester (Metvix®) has achieved high response rates in actinic keratoses and BCC, although no comparison data with ALA are published.[25,26] An open study of 94 patients with 'high-risk' BCC (mid-face, large or recurrent), for which conventional therapy was unsuitable, showed a 74% histological clearance rate and 75% good or excellent cosmetic outcome after fractionated Metvix-PDT.[27] The results of a randomized study of excision surgery vs. topical Metvix PDT for primary BCC await publication.

Reported application intervals for ALA vary from 3 to 48 h, with 4–6 h extensively studied.[14] The optimal preillumination interval is probably disease dependent; only one non-randomized comparison study is published, suggesting that a 6-h application may be superior to a 4-h one for superficial BCC up to 2 mm thick.[28]

Light sources and dosimetry

Several light sources have been used in clinical PDT studies for cutaneous applications, including lasers, xenon arc/discharge lamps, incandescent filament lamps and solid-state light-emitting diodes (LEDs). Limited randomized comparison data exist, although one study demonstrated an equivalent response of BCC to ALA-PDT with light delivered from either a copper vapour pumped dye laser or a broadband incandescent halogen source.[29] Most sources seek to utilize the 'red' 630 nm absorption peak of PpIX in order to maximize tissue penetration, although the emission of one fluorescent lamp is centred on the maximum, but least penetrating 'blue' 410 nm peak, and several broadband lamps can activate smaller peaks at 505, 540 and 580 nm (Table 2).[11] The contribution of emission wavelengths beyond 630 nm that may activate PpIX photoproducts (640–670 nm) is not known, but this probably has little therapeutic effect.[30] Comparison of light sources requires consideration of their relative efficiency, as estimated by mapping their spectral output to PpIX absorption, as well as total power, size of illumination field, ease and cost of use, and flexibility to adapt to the use of other photosensitizers.

Choice of light source may also be influenced by intended application(s). Red light may penetrate up to

Table 2. Light sources for topical 5-aminolaevulinic acid-photodynamic therapy (ALA–PDT)

Type	Specific types	Emission λ (nm)	Fluence rate (mW cm^{-2})	Maximum field diameter (cm)	Portability[a]	Flexibility[b]	Comments
Laser	Argon dye	630	10–500	10	N	Y	Laser safety requirements[c]
	Copper vapour dye	630	10–500	10	N	Y	Laser safety requirements[c]
	Nd:YAG-KTP dye	630	10–500	10	N	Y	Laser safety requirements[c]
	Semiconductor diode	630 ± 5	10–500	10	Y	N	Laser safety requirements[c]
LED array	PRP 100	630 ± 5	< 150	4	Y	N	Need to hold handpiece, (nil published)
Xenon arc	Paterson PTL	630 ± 15 (filter)	10–130	8	Y	Y	λ range 400–1200 nm
Metal halide	Waldmann 1200	600–750	10–200	15	N	Y	Suited for large area
Tungsten/ halogen	Projector (modified)	570–1100	< 200	~15	Y	Y	Low output and uncertain waveband
	Photocure Curelight	570–670	< 150	5·5	N	N	
Fluorescent	DUSA Blu-U	417 ± 5	10	> 20	N	N	U.S.A. only (August 2001)

LED, light-emitting diode. [a]Portability: can be carried between rooms/sites rather than requiring a dedicated space; [b]flexibility: potential for use with alternative photosensitizers, e.g. availability of other wavelengths; [c]beam delivery via 400-μm fibre suitable for systemic PDT.

6 mm, compared with 1–2 mm for light at 400–500 nm, depending on the tissue; however, in skin where light scatter is high, the therapeutically effective depth of ALA-PDT is likely to be considerably less, i.e. 1–3 mm at 630 nm.[5] Blue light and green light are reported to be effective in actinic keratoses,[4] with green light as effective as red light in one half-side non-randomized comparison of six patients.[31] In a randomized comparison of green with red light in Bowen's disease (61 lesions), however, green light was significantly inferior, suggesting that deeper light penetration to include skin appendages is required in Bowen's disease.[32]

Clinical protocols for topical ALA-PDT can presently be defined only in terms of explicit parameters, including the administered ALA dose (and vehicle), the drug–illumination interval, and the wavelength/band, fluence rate or irradiance (mW cm^{-2}) and fluence or dose (J cm^{-2}) of externally delivered light. Total effective fluence, taking into account incident spectral irradiance, optical transmission through tissue and absorption by photosensitizer, has been proposed as a concept for more accurate dosimetry taking account of the variety of light sources available.[33] In practice, light dosage is usually estimated from the energy fluence, due to the difficulty in determining other parameters. Comparison of dosimetry in studies using different broadband sources is thus prevented, as a significant proportion of incident light may be of relatively ineffective wavelengths.

Fluence rates greater than 50 mW cm^{-2} may begin to affect oxygen availability in ALA-PDT, and rates over 150 mW cm^{-2} may induce hyperthermic injury.[34,35] A recently described mathematical model of photodynamic damage predicts that low fluence rates can be as effective as high-rate illuminations if performed over the same time.[36] The spectral output of certain incandescent light sources, e.g. xenon arc, metal halide and tungsten/halogen, includes infrared, which is usually removed as it will contribute to tissue heating, possibly increasing the risk of scarring. Fractionation (discontinuous illumination) may improve tumour responsiveness by permitting tissue reoxygenation during 'dark' periods, although its importance in topical ALA-PDT of cutaneous malignancy has not been studied. Optimal light dose is likely also to be disease specific, with high tumour-killing doses used in NMSC (54–540 J cm^{-2}); this is in comparison with almost complete photo-oxidation (photobleaching) of psoriatic plaques observed after 16 J cm^{-2} in studies using modified slide projectors.[1,37] It is recommended that all relevant information about the source, model type, bandwidth, intensity and uniformity should be given in clinical reports.

Published studies indicate that several light sources are effective in promoting the NMSC applications of ALA-PDT (*strength of recommendation A, quality of evidence IIiii*). At present, no single light source is ideal for every possible indication for topical PDT. Choice should be based on the proposed clinical indications (including number and size of lesions), priorities for a portable compact source with a smaller field size vs. a bulky fixed large field-size source, flexibility, treatment times and cost.

Indications for topical photodynamic therapy

Actinic keratoses

In six open studies of ALA-PDT of 323 actinic keratoses situated on the face and scalp in caucasian populations, clearance rates ranged from 71 to 100% after a single treatment.[1,38–42] Itoh *et al.*[43] recently reported the efficacy of ALA-PDT for actinic keratoses in Oriental patients with a clearance rate of 82% for facial lesions, although three to six treatments were required. Jeffes *et al.*[40] noted no difference in response between 10% and 30% preparations of ALA, with application times typically ranging from 3 to 6 h. Several lamps have been used, but even in the two studies that employed two light sources, no randomization was performed and dosimetry differed, preventing comparison.[41,43] Green light may be as effective as red for actinic keratoses,[31] with less pain reported. A blue light source (Blu-U®, delivering 10 J cm^{-2} at 10 mW cm^{-2}) is licensed for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp, with an ALA formulation (Levulan Kerastick®) applied 14–18 h prior to illumination. A complete clearance rate for patients of 66% after one treatment is reported, rising to 72% by 12 weeks following a second treatment, where required.[4]

Four studies report the inferiority of response of acral actinic keratoses in comparison with facial lesions, with weighted clearance rates of 44% (105 of 240) compared with 91% (286 of 315).[39,40,43,44] Kurwa *et al.*[45] compared ALA-PDT with topical 5-fluorouracil in a randomized comparison study of 17 patients with extensive disease affecting both hands. The reduction in lesional area on the hand randomized to a single treatment with ALA-PDT (73%) was almost identical to that following 5-fluorouracil application (71%). Histopathological confirmation of clearance is rarely undertaken, although Calzavara-Pinton[46] observed persisting disease in three of 17 apparently clear sites histologically sampled in a study of 50 lesions. He followed up patients for 24–36 months, recording a 10% recurrence rate. Szeimies *et al.*[47] performed a randomized multicentre comparison of 699 actinic keratoses using methyl 5-aminolaevulinate-based PDT in comparison with cryotherapy. Of the actinic keratoses studied, 93% were thin or of moderate thickness and 92% were situated on the face or scalp. Overall response rates, at 3 months, to a single treatment session were similar between the groups (69% for PDT, 75% for cryotherapy), but cosmetic outcome was superior in the PDT group.

ALA-PDT, and possibly also methyl 5-aminolaevulinate-PDT, are effective in clearing non-hyperkeratotic actinic keratoses on the face and scalp, with response rates comparable with topical 5-fluorouracil and cryotherapy, although with a cosmetic response superior to that with cryotherapy (*strength of recommendation A, quality of evidence I*).

Bowen's disease

Topical PDT using 20% ALA has been extensively assessed in Bowen's disease [squamous cell carcinoma (SCC) *in situ*] with 13 open (pilot and case series)[1,7,20,46,48–56] and three randomized comparison studies.[32,57,58] A single ALA-PDT treatment cleared 86% (weighted complete clearance rate, six studies, 71 of 83), rising to 93% (nine studies, 239 of 257) of lesions if one or two repeat treatments were permitted in the protocol. The recurrence rate ranged from 0 to 40%, average 12%, during follow-up periods of 3–36 months. Most studies were small, with seven of 16 treating only three to 10 lesions. Protocols differed, with laser, tungsten, xenon and LED sources used. An application time of ALA of 3–6 h was widely practised, with extension to 20 h in one study in which only five of 10 patches of Bowen's disease were cleared.[20] ALA-PDT is also effective in the closely related entity erythroplasia of Queyrat, with a case series reporting clearance in two patients and partial response in another two who had more extensive disease.[59] The subsequent development of an SCC at the treatment site in a separate case report (see below) emphasizes the need for close follow-up.[60]

The optimum wavelengths for treating Bowen's disease are not defined, although the preference for more penetrating red light is supported by a randomized comparison study of 59 lesions, which demonstrated a significantly higher clearance rate with red light (630 ± 15 nm) than green (540 ± 15 nm).[32]

Two randomized studies compared topical ALA-PDT with conventional therapy.[57,58] ALA-PDT was at least as effective as cryotherapy (one or two PDT visits, one to three cryotherapy visits) in clearing 20 small patches of Bowen's disease. PDT demonstrated a significantly higher rate of clearance after a single treatment (75% vs. 50%).[57] Adverse events were only observed in the cryotherapy group: ulceration (five of 20), infection (two of 20) and scar formation (four of 20). A randomized trial comparing ALA-PDT with topical 5-fluorouracil (one or two treatment cycles in each

group) showed that PDT was also at least as effective at 8 months follow-up, with fewer adverse reactions.[58] No comparison data with radiotherapy, surgery or curettage exist.

Topical ALA-PDT may be particularly useful for large and multiple patches of Bowen's disease. The clearance, by ALA-PDT, of three large patches of Bowen's disease, 40–80 mm in diameter, has been supported by a recent study of 40 large (20–55 mm) lesions.[52,56] An initial clearance rate of 88% after one to three treatments fell to 78% by 12 months. In the same study, 10 patients with 45 patches of Bowen's disease saw an overall clearance rate with PDT of 89% after 12 months. The absence of serious adverse events and observed good cosmesis were again noted.

In summary, ALA-PDT is effective in Bowen's disease, achieving good cosmesis, and is at least as effective as cryotherapy or 5-fluorouracil, but with fewer adverse events. Topical PDT may offer advantages over existing modalities for large or multiple lesions, those in poor healing sites such as the lower leg, and for penile, digital and facial lesions where existing treatments have recognized limitations (*strength of recommendation A, quality of evidence I*).

Basal cell carcinoma

The weighted average complete clearance rates, after follow-up periods of 3–36 months, were 87% and 53%, respectively, in 12 studies treating 826 superficial and 208 nodular BCCs reviewed by Peng *et al.*[34] For tumours up to 1 mm thick, initial clearances of 81% (26 of 32), 95% (59 of 62) and 100% (36 of 36) were reported after one or two treatments (4–6 h ALA application), although with recurrence rates by 12–24 months of 16%, 18% and 6%, respectively.[28,36,55] Limited data on the depth of response are available for thicker superficial BCCs, although six of six up to 2 mm thick, treated at 6 h, cleared without recurrence over 6–16 months.[28] Morphoeic and pigmented lesions respond poorly to PDT.[34]

The inferior response of nodular BCCs, with their lack of homogeneous uptake of photosensitizer,[13,14] led Warloe *et al.*[21] to perform a non-randomized comparison of ALA-PDT with penetration enhancers. DMSO + EDTA increased clinical clearance rates from 67% to 90% for nodular BCCs < 2 mm, and from 34% to 50% for thicker lesions. Prior debulking curettage by Thissen *et al.*,[22] 3 weeks pre-PDT, achieved a 92% clinical and histological response rate in 24 nodular BCCs when all treated skin areas were excised at 3 months. Soler *et al.*[61] similarly cleared 92% of 119 nodular lesions by penetration enhancement and curettage, with 95% of lesions remaining clinically clear after 17 months (range 12–36). Prior surface shaving probably also enhanced response rate to 90% in 10 nodular BCCs treated by PDT with ALA methylester applied for 3 h.[26]

Only one randomized comparison study has been published of ALA-PDT with cryotherapy for both superficial and nodular BCCs, with no significant difference in efficacy, although with fewer adverse events, shorter healing times and superior cosmesis following PDT.[62] Caution in interpreting short-term follow-up studies is advised following the observation in this study of a recurrence rate following PDT at 12 months, by clinical examination of 5%, but of 25% when verified by histopathology at the same visit. Presently, there are no 5-year follow-up data, and, therefore, no direct comparison of ALA-PDT can be made with conventional therapies.[63]

A complete clearance rate of 96% at 12 months for superficial BCC has suggested the importance of technique, with a double treatment 7 days apart yielding results superior to the same group's 50% complete clinical response rate after a single treatment.[48,64] Patients with large and multiple superficial BCCs may particularly benefit from topical PDT,[53,55,56] although the response of patients with naevoid basal cell epithelioma syndrome has been disappointing with only 11 of 18 (61%) superficial tumours and 3 of 26 (12%) nodular lesions clearing in one study.[21]

Guidelines published by the British Association of Dermatologists in 1999 on the treatment of BCC list excision or cryotherapy as the treatments of choice for most presentations.[3] PDT was considered an investigational tool that probably should not be used in BCC. Although licensing for BCC treatment is awaited, current evidence indicates topical ALA-PDT to be an effective therapy for superficial (<2 mm thick) BCC, at least as effective as cryotherapy, but with superior healing and cosmesis, and with particular advantages in large and multiple lesions (*strength of recommendation A, quality of evidence I*). Topical ALA-PDT is, less effective for nodular BCC, and although adjunctive therapy with prior curettage or with penetration enhancers, or fractionated treatment may improve results, there is no published randomized evidence of their benefit (*strength of recommendation C, quality of evidence IIiii*).

Squamous cell carcinoma

In three open studies[46,53,63] of topical PDT in the treatment of SCC, there was an initial response rate of 54–100% (69% weighted average; 52 of 75) for superficial lesions, but recurrence rates of up to 69% (average 24%; 12 of 49) after 3–47 months. Only four of 10 'nodular' tumours remained clear after 12–36 months.[46,53] Fritsch *et al.*[53] achieved a 79% clearance rate after 12–24 months in 28 superficial lesions. Calzavara-Pinton[46] clinically cleared 92% (11 of 12) of superficial SCCs, 6–8 h after ALA application, with a pathologically confirmed clearance rate at 24–36 months of 83%. Fink-Puches *et al.*[63] treated 35 superficial SCCs with ALA followed by exposure to either ultraviolet A or different wavelengths of polychromatic visible light. A complete response with all wavelengths of light was obtained for 54%, but with a 69% recurrence rate after a mean follow-up of 8 months (range 3–47). Despite a few encouraging results, in view of its metastatic potential and high recurrence rates, caution is currently advised in using topical ALA-PDT to treat SCC (*strength of recommendation D, quality of evidence IIIii*).

Applications for topical 5-aminolaevulinic acid-photodynamic therapy other than in non-melanoma skin cancer

Topical PDT has been applied in small case series, with encouraging results in actinic cheilitis,[65] condylomata acuminata,[66] keratoacanthoma,[46] lichen sclerosus[67] and scleroderma.[68] There are isolated reports of efficacy in the treatment of epidermodysplasia verruciformis,[69] hirsutism,[70] lichen planus,[71] naevus sebaceus[72] and others. Disappointing results have been seen with topical PDT for breast cancer metastases[1,48] and malignant melanoma.[38] The use of topical PDT in the treatment of vulval intraepithelial neoplasia (VIN) indicates benefit with multiple treatments,[73] with histological grade of VIN as a determinant of response,[74] and lack of response with single-treatment PDT for VIN type III.[75] The use of topical PDT as monotherapy for extramammary Paget's disease is controversial as reports are mainly in combination with other therapies;[76] however, clearance of recurrent disease with intralesional ALA and multiple treatments has been shown in one subject.[77] In view of limited evidence, no recommendations are proposed concerning the above indications, except for breast metastases and VIN, where there is currently poor evidence to support its use (*strength of recommendation C, quality of evidence IIiii*). A recent randomized controlled trial has demonstrated a lack of effect of ALA-PDT in alopecia areata[78] (*strength of recommendation D, quality of evidence I*).

Most studies on non-NMSC applications for ALA-PDT concern warts, acne, psoriasis and cutaneous T-cell lymphoma (CTCL) (Table 3).

Warts (strength of recommendation B, quality of evidence I)

Despite a report of lack of efficacy of single-treatment ALA-PDT in the treatment of viral warts,[79] subsequent case series and comparison trials reported by Stender *et al.*[80–83] achieved clearance rates of 56–100%, and demonstrated superior efficacy of repetitive ALA-PDT compared with cryotherapy or placebo-PDT. In a comparative study, white light PDT was more effective than red or blue light PDT or cryotherapy in patients with refractory warts and verrucas.[81] A subsequent, randomized study demonstrated superior efficacy of ALA-PDT compared with placebo-PDT, with endpoints of significant reduction in the wart area and increased rate of clearance with the active treatment group.[83] However, a significant side-effect of treatment was pain, which may limit use, particularly in children. Successful PDT to recalcitrant warts would appear also to require lesion paring pretreatment, with additional paring with or without topical keratolytic treatment during the study period.

Acne (strength of recommendation B, quality of evidence I)

A recent study in patients with mild to moderate acne showed superior efficacy of a combination of red and blue light phototherapy in improvement of both comedonal and inflammatory acne.[84] Although treatment was without the use of an exogenous photosensitizer, the mechanism of action is likely to include endogenous PDT of porphyrins in *Propionibacterium acnes*. The use of ALA-PDT has been examined in an open placebo-controlled study in 22 subjects with moderate truncal acne, showing reduction in sebum production, *P. acnes* fluorescence, sebaceous gland size and clinical acne for up to 20 weeks after multiple treatments.[85] Furthermore, Itoh *et al.* reported prolonged benefit for several months after low-dose, single-treatment ALA-PDT.[86,87] These findings provide encouraging evidence that ALA-PDT may be a useful adjunct in certain types of acne, but discomfort during treatment, crust formation, erythema and

Table 3. Summary of studies using 5-aminolaevulinic acid-photodynamic therapy (PDT) in warts, acne, psoriasis and cutaneous T-cell lymphoma (CTCL)

Condition	Study design	No. of patients (lesions)	No. of PDT treatments	Clearance no. (%)/outcome	Recurrence rate (follow up, mo)	Comments
Warts	CS[79]	6	1	1/6 (17%)	0 (2)	No lesion preparation
	CS[80]	4	2–3	4/4 (100%)	0 (12–14)	Lesions pared pre-PDT
	RCT[81]	30 (250)	3	41/56 (73%)	0 (12)	Cryotherapy: 20% CCR
	CS[82]	62	3	30/52 (58%)	0 (3–17)	10 drop-outs due to pain
	RCT[83]	45 (232)	3–6	64/114 (56%)	N/K	PDT superior to placebo
Acne	RCT[85]	22	1 or 4	All improved	Response to 5 mo	Reduced sebum for 20 weeks
	CR[86]	1	1	Cleared	Response to 8 mo	Combined with peel
	CS[87]	13	1	All improved	Response to 6 mo	
Psoriasis	CS[88]	3	3	All responded	Response to 6 mo	Equivalent efficacy to dithranol
	CS[90]	14 (84)	1, 4	Improvement	Response to 2 mo	Improvement in lesion severity
	PS[37]	22 (80)	1	10/36 (28%)	100% by 14 days	2-cm^2 sites within plaques treated
	PS[92]	10 (19)	7–12	1/19 (5%)	0 (4)	13/19 partial response
CTCL	CS[94]	2 (3)	4–5	3/3[a] (100%)	33% (8–14)	All plaques
	CS[7]	2 (4)	1, 2	2/4 (50%)	0 (6–14)	All plaques
	CR[95]	1 (1)	1	0	N/A	Clinical, but not histological clearance
	PS[96]	N/K	N/K	Efficacy	N/K	CCRs obtained in all stages
	CR[97]	1 (1)	1	1/1 (100%)	0 (12)	Single 14-cm diameter plaque
	CR[98]	5 (6)	1–2	0	N/A	4 clinically clear, 0 clear on histology
	CS[99]	1 (3)	3 (median)	3/3 (100%)	0 (12)	
	CR[100]	1 (1)	5	1/1[a] (100%)	0 (12)	1 tumour-stage lesion
	CS[101]	2 (6)	1–2	6/6 (100%)	0 (24–27)	1/6 patch, 5/6 thick plaque

CR, case report; CS, case series; PS, pilot study (clinical efficacy not principal aim); RCT, randomized comparison study; N/A, not applicable; N/K, not known; CCR, complete clinical response; mo, month(s). [a]Histological confirmation of clearance.

pigmentation for up to 4 weeks after treatment may limit patient acceptance of this therapy.

Psoriasis (strength of recommendation C, quality of evidence IIiii)

Photobleaching during topical PDT for psoriasis is established, and the same authors demonstrated efficacy of three times weekly topical PDT comparable with dithranol.[88,89] Subsequent studies have shown marked variation in PpIX fluorescence in psoriatic plaques after ALA application and in treatment response and discomfort experienced.[37,90,91] Multiple treatments improved clinical outcome, although this remained unpredictable and pain was a limiting factor.[92] At present, the optimal regimen for topical PDT for psoriasis has not been established and the limitations of variation in photosensitizer accumulation, therapeutic response and pain preclude its use in clinical practice.

Cutaneous T-cell lymphoma (strength of recommendation C, quality of evidence IIiii)

Selective uptake of photosensitizers into lymphocytes after topical PDT, with inhibition of T cells and photobleaching, has been demonstrated in topical PDT of CTCL using a mixture of porphyrins, including PpIX.[93] Repetitive treatments with topical ALA-PDT resulted in clinical and histological remission in two patients with plaque-stage CTCL but, in another case, clinical but not histological clearance was observed after one treatment, emphasizing the probable need for multiple treatments.[94,95] This has been supported by others, showing that, despite a tumour/normal tissue fluorescence ratio of 5 : 1, a response rate of only 50% was obtained with a single ALA-PDT treatment.[7] Other small studies are summarized in Table 3.[96–101] The optimal regimen for treatment has yet to be established.

Adverse effects

Acute

Pain or discomfort, often described as 'burning', 'stinging' or 'prickling' restricted to the illuminated area[102,103] is commonly experienced during ALA-PDT. It usually occurs in the early part of light exposure, peaking within minutes, then levelling out during the remainder of exposure, and probably reflects nerve stimulation and/or tissue damage by reactive oxygen species. This discomfort can occasionally persist for hours, and rarely for a few days, at a reduced intensity. Most patients will, however, tolerate topical

ALA-PDT without anaesthesia/analgesia.[38,46,57] Few clinical trials have carefully monitored pain, but the face and scalp may be more susceptible, and large and/or ulcerated lesions are more likely to be painful.[28,44,56] Topical PDT of psoriasis and viral warts is frequently associated with pain (see above). While pain may be related to PDT dose, no linear relationship has been identified.[37] Hyperthermia may contribute to tissue damage and thus intensify pain.[104] The wavelength of light may influence pain severity, with green light less painful than red in a study of facial actinic keratoses.[31] Such difference in pain was, however, not noted in a randomized comparison of green and red light in Bowen's disease.[32] Comparison studies indicate that the pain associated with ALA-PDT is less severe than that induced by cryotherapy and is equivalent to the total pain induced by topical 5-fluorouracil application.[45,57,58,62]

Strategies to reduce pain include prior topical/injected local anaesthetic, premedication with benzodiazepine, cooling fans or spraying water on lesions during therapy.[48,52,56,61,102] As ALA, but not ALA methylester, is transported by γ-aminobutyric acid carriers, it is speculated that the ester might be less likely to provoke nerve fibre stimulation and hence pain.[105] There remains no direct clinical comparison of these photosensitizers to test this hypothesis, nor of the different methods of alleviating pain.

Immediately following illumination, erythema and oedema are common, with erosion, crust formation and healing over 2–6 weeks.[7,37,63,103] Unlike cryotherapy or topical 5-fluorouracil, ulceration following PDT is very rare.[57,58] No generalized photosensitivity has been reported following topical ALA-PDT in NMSC, and ALA-induced PpIX appears to be almost completely cleared from the body within 24 h of its induction.[16,106]

Chronic

A good cosmetic outcome following ALA-PDT is widely reported, regardless of lesion or site, in comparison with conventional therapy as supported by blinded clinical assessment.[62] A clinically obvious scar is rarely observed, although Fink-Puches *et al*. observed histological evidence of scarring.[63] Hyperpigmentation or hypopigmentation can occasionally be seen in treated areas and usually resolves within 6 months, although prolonged hyperpigmentation was observed when treating hirsutism.[31,52,70,83,106] Permanent hair loss has been observed following ALA-PDT. In a patient with extensive scalp BCC, the local thinning over lesions was mild and much less than that following radiotherapy to an adjacent lesion.[107] Hair loss has been observed following ALA-PDT to large patches of Bowen's disease and BCC on non-scalp sites.[52,56]

Carcinogenicity

PDT has the potential of promoting genotoxic effects, including induction of DNA strand breaks, chromosomal aberrations and alkylation of DNA.[108–111] However, porphyrin molecules also possess antimutagenic properties, with ALA-PDT delaying photocarcinogenesis in mice.[112] Following over 25 years of experimentation with PDT in humans, and 10 years of ALA-PDT, only two tumours have possibly been induced by this therapy.[60,113] The first case concerns an 82-year-old man who had received, over 4 years, seven sessions of ALA-PDT to treat actinic keratoses and SCCs. Six months following his last treatment, a melanoma was identified at a site that had been included in four of the PDT sessions. Although possibly coincidental, there is the potential that repetitive treatments of PDT may have promoted its development. Recently, a 38-year-old man with erythroplasia of Queyrat appeared to have responded to ALA-PDT, with clearance on three post-therapy biopsies.[60] Clinical doubt over completeness of clearance led to his commencement on topical 5-fluorouracil (twice weekly for 4 months), but an SCC was subsequently identified when a nodule developed on the penis. This case may represent simple progression of residual erythroplasia to SCC, but the possibility that PDT promoted this progression requires consideration. Overall, available evidence would indicate that the risk of skin cancer associated with topical PDT is low, but in view of the latent period for carcinogenesis, long-term follow-up data are required.

ALA-PDT has a low frequency of severe adverse effects, achieves a good cosmetic outcome, and has a low risk of carcinogenicity (*strength of recommendation B, quality of evidence IIiii*).

Safety aspects of topical photodynamic therapy

Topical PDT treatments are intrinsically very safe. The relative specificity of the photosensitizer to abnormal cells, taking some hours' application to be effective, and the use of lower energy radiation (normally in the visible spectrum), reduce the potential hazards. Accidental exposure to the photosensitizer carries a low risk, as washing removes it almost completely, and

any residue is unlikely to be activated by normal environmental light levels.

Potential hazards may arise from the use of surgical lasers to deliver high-intensity light to photosensitized skin, and radiation in the blue, ultraviolet or infrared wavelengths may pose a greater potential hazard to skin and eyes. The lower energy visible radiation is much safer for the skin than ultraviolet, but there are potential hazards to the eye arising from the high intensities employed.[114] The retina is at risk from the photochemical hazard of blue light (400–450 nm), which could irreversibly damage the photosensitive neurotransmitters in the macula.[115] Most ALA-PDT is conducted at longer red bandwidths, but staff and patients are advised to wear suitable filter spectacles to limit the transmission of the high-intensity light, and to avoid discomfort and the disturbance of colour perception that can arise from intense exposure to a limited colour bandwidth.

Most radiation sources in use for dermatology presently are non-coherent incandescent or discharge lamps, but laser systems or LED arrays are sometimes used. Any laser system classified as class IIIb or IV (most medical lasers) is subject to the Laser Protection Guidelines. A certified Laser Protection Adviser should be consulted prior to the use of such a device. Modern LED devices have small source dimensions and high brilliance, but under normal conditions of use they should pose no significant increase in risk to the skin or eyes.[116]

Cost assessment of topical photodynamic therapy and comparison with existing therapy

In addition to clinical efficacy, assessment of cost-effectiveness is an important aspect of determining the overall benefit offered by a new therapy such as PDT. Such an assessment requires estimation of staff and equipment costs combined with number of treatments required, expectation for clearance, costs of associated morbidity, and diagnostic and follow-up requirements. Comparison of these figures with those from conventional therapy is limited by a deficiency of accurate data and difficulty placing a cost on certain outcome measures such as the relative superiority of PDT for good cosmesis. Estimated costs for treating patients with a single NMSC lesion with ALA-PDT are shown in Appendix 2. Medical staff time would be required for an initial clinic assessment and follow-up but as these are also required for the alternative treatment options, these costs have been omitted from the current calculations. Bell and Rhodes[117] observed that up to eight visits (median 4) were required to clear lesions of Bowen's disease in 68 patients presenting to one U.K. dermatology department employing a range of treatment options other than PDT. An efficiently organized ALA-PDT service offers the potential for reducing the number of visits and hence the cost of managing this disease (Appendices 3, 4). Available estimates for cost-effectiveness indicate ALA-PDT to be generally comparable in cost with other therapies when morbidity costs in standard treatments are included, becoming more economical where multiple lesions can be treated in one irradiation field.

Conclusions

Many, typically open, uncontrolled studies indicate ALA-PDT to be effective in certain clinical applications (Appendix 5), particularly in actinic keratoses affecting the face and scalp, Bowen's disease and superficial BCC. Randomized comparison studies indicate PDT to be at least as effective as existing therapies for these indications. Cost-effectiveness analysis suggests that with relatively cheap equipment costs, topical ALA-PDT is probably no more expensive than conventional therapy when its lower side-effect profile is considered. ALA is the predominant photosensitizer used. Early work indicates that its methyl ester derivative is also effective, although no comparison data exist. Several light sources are effective in delivering ALA-PDT. Certain lamps are more efficient at delivering the longer wavelengths considered optimal particularly for deeper lesions, although lack of direct comparison limits assessment of superiority. Contacts for photosensitizer and light sources are listed in Appendix 6.

ALA-PDT for non-hypertrophic actinic keratoses on the face and scalp and Metvix-PDT for BCC 'unsuitable for conventional therapy' is already approved (U.S.A. and Sweden), with European approvals in NMSC anticipated shortly. Caution is advised in considering topical PDT for thick/nodular BCC, unless with modifications such as adjunctive or fractionated therapy or for squamous cell carcinoma. Additional applications remain at the experimental stage, with early potential suggested in refractory warts and acne. We note that several large multi-centre studies on topical PDT with methyl-ALA and ALA are underway worldwide and are expected during the next 5 years to improve the quality of available evidence in specific indications.

Note added in proof

In December 2001, approval was granted for actinic keratoses and basal cell carcinomas in 14 European countries, including the U.K. for topical PDT using methyl 5-aminolevulinate-PDT (metvix®).

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Appendix 1: Strength of recommendations and quality of evidence

Strength of recommendations

A There is good evidence to support the use of the procedure.
B There is fair evidence to support the use of the procedure.
C There is poor evidence to support the use of the procedure.
D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.
IIi Evidence obtained from well-designed controlled trials without randomization.
IIii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
IIiii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology.

Appendix 2: Cost comparison of topical 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) with standard therapy

Estimated for a patient presenting to the U.K. National Health Service, with a 2 × 2 cm plaque of Bowen's disease. Based on published clearance/morbidity rates[57,58] with average costs derived from out-patient healthcare resource group codes.[118]

1 ALA-PDT: £119 (assumes two treatments to clear 25% of lesions + 4% recurrence rate with clearance on repeat treatment). Single therapy cost breakdown:
(a) Light: £53 (averaged cost of the two sources most widely reported in the literature: (i) Paterson PTL, leased and using smartcard: £80 per lesion; (ii) Waldmann 1200: cost £11697, maintenance £400 per year for years 2–5, excluding replacement of filter + lamp at 500 h @ £ 2444, assuming 5-year life and use to clear 100 lesions per year: £27 per lesion).
(b) Photosensitizer: £24 (£70 for 4·5 g Porphin cream, three lesions per tube possible if multiple lesions are treated each day and measures taken to avoid cross-infection).
(c) Nursing: £10 (grade E, 1 h).
(d) Consumables: £5 (dressings, local anaesthesia etc.) = Total: £92 per single treatment.
2 Cryotherapy: £145 @ £64 per treatment, 50% of lesions require two or three treatments and 10% recurrence (assuming one successful retreatment). Estimated 'complication' cost to cover ulceration and/or infection rate of 25% assumes one additional

dressing visit @ £68 and one extra review visit @ £50 per complication but excludes district nurse/general practitioner visit costs and dressing/topical therapy cost for each complication).[57]

3 Topical 5-fluorouracil: £171 @ £68 per treatment cycle (£50 per visit + £18 for topical 5-fluorouracil), 33% clear on one cycle, 30% on two, 30% failures (assume then cleared with single cryotherapy), 27% recurrence rate (assume then clear with one further cycle), complication rate (including ulceration and severe dermatitis) of 30% at same cost per complication as cryotherapy).[58]

Appendix 3: Outline protocol for topical 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) in non-melanoma skin cancer

1 Out-patient assessment: record diagnosis (consider biopsy and photography), number, size and site of lesions, additional medical diseases and current medication, required treatment regimen (photosensitizer duration, single/double treatment).

2 Provision of patient with information sheet and consent in clinic or at treatment.

3 Attendance to dermatology treatment unit for lesion preparation (e.g. removing crusts with gauze soaked in saline, with or without forceps) and application of ALA preparation, including 5-mm margin around lesion. Application of an adhesive dressing to retain cream at site (e.g. Tegaderm, 3M, Loughborough, U.K.) plus a dressing to minimize ambient light exposure (e.g. Mepore, Molnlycke Health Care, Sweden).

4 Patient then returns 4–6 h later, for removal of excess cream and optional check of surface fluorescence with an ultraviolet Woods' lamp (e.g. UVL-56, Upland, CA, U.S.A.)—helpful in confirming protoporphyrin IX generation at least in superficial part of lesion.

5 Option for either pretreatment application of a topical anaesthetic, e.g. EMLA cream (Astra, King's Langley, U.K.), applied following removal of excess ALA 1 h prior to illumination (i.e. at 3–5 h), or provision during illumination, if required, of local injected anaesthesia, e.g. 1–2% lignocaine (plain suggested to minimize possible vasoconstricting effects of adrenaline on PDT efficacy).

6 Illumination of lesion to a lamp-specific protocol, with illumination field including a border around each lesion of at least 5 mm. Ensure that the correct position of light is maintained. Total light dose and intensity of illumination should be recorded.

7 Protect treatment site from ambient light for up to 24–48 h.

Appendix 4: Setting up a topical photodynamic therapy (PDT) service (preparing the business case)

1 Define the clinical need: estimation of number of suitable patients and current management approach, taking into consideration rising non-melanoma skin cancer prevalence, complications and patient perceptions of existing therapies; local audit and pathology data helpful.[117,119]

2 Describe topical PDT and its uses, its potential advantages over existing therapies, including estimated savings (e.g. reduced ulceration).

3 Include protocol and description of patient journey if new service implemented.

4 Costing PDT:

(a) Site (dedicated room vs. sharing out-patient treatment centre facilities, specific adaptations if laser source considered).

(b) Staffing: (i) medical (supervision of service, but low real-time requirement other than diagnostic and follow-up visits if performed to protocol, with clinic referral to day/phototherapy unit); (ii) nursing (hours of dermatology nurse specialist time—grade to depend on local expertise, but ability to perform entire procedure, including local anaesthesia, if required, preferable); (iii) medical records (appointments, case records—potential for similar set-up to other phototherapies).

(c) Equipment: (i) light source (purchase vs. lease, maintenance costs); (ii) photosensitizer (cost per lesion vs. drug unit cost); (iii) disposables, e.g. dressings.

5 Training: time required and arrangements proposed for training staff to become competent in PDT.

6 Proposals for prospective audit of new service.

Appendix 5: Strength of recommendations and quality of evidence assessment

A–IIiii A range of light sources is effective in promoting dermatological applications of 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT).

B–IIiii Topical ALA-PDT is a safe treatment with few side-effects and no evidence of carcinogenicity during a decade of clinical use.

A–I Actinic keratoses (non-hyperkeratotic, face and scalp).
A–I Bowen's disease (squamous cell carcinoma *in situ*).
A–I Superficial basal cell carcinoma (BCC) (thickness < 2 mm).
B–I Acne.
B–I Warts.
C–IIiii Thick/nodular BCC
C–IIiii Cutaneous T-cell lymphoma.
C–IIiii Cutaneous metastases of breast carcinoma.
C–IIiii Psoriasis.
C–IIiii Vulval intraepithelial neoplasia.
D–I Alopecia areata.
D–IIiii Squamous cell carcinoma.

Appendix 6: Contacts for photosensitizer [5-aminolaevulinic acid (ALA)] and light sources

ALA (Porphin®): Crawford Pharmaceuticals, Furtho House, 20 Towcester Road, Old Stratford, Milton Keynes MK19 6AQ, U.K.

ALA (Levulan Kerastick® and Blu-U® lamp): registered to DUSA Pharmaceuticals, Inc., Wilmington, MA, U.S.A. European contact: Schering AG, Centre of Dermatology, D-13342 Berlin, Germany.

ALA-methylester (Metvix®): Photocure ASA, Hoffsvn. 48, N-0377 Oslo, Norway. Outside Nordic countries, contact: Galderma SA, Tour Europlaza, La Defence 4, 20 avenue Andre Prothin, F-92927, La Defence cedex, France.

Paterson Lamp: Phototherapeutics Ltd, Station Business Centre, Station House, Stamford New Road, Altrincham, Greater Manchester WA14 1EP, U.K.

Light-emitting diode source: PRP Optoelectronics Ltd, Wood Burcote Way, Towcester NN12 7HT, U.K.

Waldmann PDT 1200 light source: Waldmann, U.K., c/o Athrodax, Great Western Court, Ross-on-Wye HR9 7XP, U.K. or Peter-Henlein-Strasse 5, D-78056 Villingen-Schwennigen, Germany.