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Guidelines for topical photodynamic therapy: update

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Summary

Multicentre randomized controlled studies now demonstrate high efficacy of topical photodynamic therapy (PDT) for actinic keratoses, Bowen's disease (BD) and superficial basal cell carcinoma (BCC), and efficacy in thin nodular BCC, while confirming the superiority of cosmetic outcome over standard therapies. Long-term follow-up studies are also now available, indicating that PDT has recurrence rates equivalent to other standard therapies in BD and superficial BCC, but with lower sustained efficacy than surgery in nodular BCC. In contrast, current evidence does not support the use of topical PDT for squamous cell carcinoma. PDT can reduce the number of new lesions developing in patients at high risk of skin cancer and may have a role as a preventive therapy. Case reports and small series attest to the potential of PDT in a wide range of inflammatory/infective dermatoses, although recent studies indicate insufficient evidence to support its use in psoriasis. There is an accumulating evidence base for the use of PDT in acne, while detailed study of an optimized protocol is still required. In addition to high-quality treatment site cosmesis, several studies observe improvements in aspects of photoageing. Management of treatment-related pain/discomfort is a challenge in a minority of patients, and the modality is otherwise well tolerated. Long-term studies provide reassurance over the safety of repeated use of PDT.

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Conflicts of interest

CAM has received honoraria for speaking, organized educational events and conducted research for Galderma, PhotoCure and Phototherapeutics Ltd.

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Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Photodermatology Group and the British Association of Dermatologists and are based on the best data available at the time the report was prepared. Caution should be exercised when interpreting data where there is a limited evidence base; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Introduction

This article represents a planned regular updating of the original guidelines for the use of topical photodynamic therapy (PDT).[1] Detailed discussion of studies evaluated in the previous paper will not be repeated except where comparison with new evidence is necessary. This may entail a disproportionate weight being given to more recent techniques and studies,

but strength of evidence recommendations (see Appendix 1) take into account all available information.

Topical PDT has, to date, been approved by regulatory authorities in 18 countries worldwide, for use in at least one nonmelanoma skin cancer (NMSC) indication. Two photosensitizing agents are licensed, a formulation of 5-aminolaevulinic acid (ALA), Levulan (DUSA Pharmaceuticals, Wilmington, MA, U.S.A.) for actinic keratosis (AK), and an esterified formulation, methyl aminolaevulinate (MAL), Metvix® (Photo-Cure ASA, Oslo, Norway and Galderma, Paris, France) for AK, Bowen's disease (BD), and superficial and nodular basal cell carcinoma (BCC). Although only one formulation of ALA currently has a licence, other preparations have been used in clinical studies reviewed here. Hence, 'Levulan ALA' will be used in this update to denote when the licensed product has been used, and 'ALA' for all other formulations.

Interventional procedure guidance from The National Institute for Health and Clinical Excellence recently concluded that there was evidence of efficacy for topical PDT in AK, BD and BCC, but limited evidence for invasive squamous cell carcinoma (SCC). No major safety concerns were observed for the use of PDT in NMSC.[2]

The past 5 years has seen publication of studies of long-term response rates of topical PDT in NMSC as well as evaluation of its potential as a preventive therapy for cutaneous malignancy. Several noncancer indications have been the focus of intense study, in particular, acne and photorejuvenation. In this update, we review the evidence for the use of topical PDT in all reported dermatological indications and interpret how this modality might best be used in clinical practice, using the same validated scoring system as in the previous guidelines.[1]

Photosensitizing agents

ALA and its methylated ester MAL are prodrugs that are endogenously converted by the haem biosynthetic pathway to protoporphyrin IX (PpIX) and potentially other intermediate photosensitizing porphyrins. These agents are relatively selectively concentrated in the target tissue, possibly related to alterations in surface permeability and tumour porphyrin metabolism.[1] Initial clinical experience of topical PDT was gained through the use of ALA, largely through case series studies. However, following publication of our initial guideline report, intensive study of MAL has led to better characterization of this prodrug and publication of its use in several randomized studies.

As ALA is hydrophilic and the esterified form MAL is more lipophilic, it was anticipated that MAL may penetrate more deeply into lesions. Peng *et al.*[3] reported that MAL penetrated to a 2-mm depth in BCC, contrasting with more limited penetration with ALA.[4] Other investigators also found highly variable ALA uptake into nodular and infiltrating BCC.[5] However, Ahmadi *et al.*[6] showed in an *in vitro* study of human skin biopsies that ALA applied for 4 h penetrated to a depth of at least 2 mm from the lesion surface. Interestingly, using similar protocols, ALA is reported to result in higher PpIX levels than MAL, but with less selectivity for the diseased compared with healthy tissue, in both AK[7] and inflammatory acne lesions.[8] Two recently reported small studies have attempted to compare the efficacy of MAL-PDT and ALA-PDT in diseased tissue, with application of each prodrug for 3 h.[8,9] Patients with nodular BCC were randomly assigned to either ALA-PDT ($n = 22$) or MAL-PDT ($n = 21$) (ALA/MAL 3 h, 600–730 nm, 75 J cm^{-2}, 100 mW cm^{-2}); in each group half the tumours were debulked prior to PDT.[9] On histological analysis after 8 weeks, no difference was found in lesional response. In a split-face comparison of 15 patients with inflammatory acne, no difference was found between ALA-PDT and MAL-PDT (ALA/MAL 3 h, 632 nm, 37 J cm^{-2}, 34 mW cm^{-2}) regarding treatment efficacy, whereas ALA-PDT resulted in more severe adverse effects after treatment.[8] A further randomized double-blind study compared ALA and MAL for the treatment of extensive scalp AK.[10] MAL was applied for 3 h, but ALA for 5 h (580–740 nm, 50 J cm^{-2}, 50 mW cm^{-2}). No significant difference in mean lesion count reduction was observed 1 month after treatment, although pain was more intense on the ALA side.

Recommendation: Topical application of the prodrugs ALA and MAL is effective in cutaneous PDT (*Strength of recommendation A, Quality of evidence I*).

Light sources and dosimetry

A range of light sources, reviewed in the 2002 guideline report, remains in use for topical PDT including lasers, filtered xenon arc and metal halide lamps, fluorescent lamps and light-emitting diodes (LEDs). Nonlaser light sources are popular in topical PDT, possessing the advantages over lasers of being inexpensive, stable, easy to operate, requiring little maintenance, and providing wide area illumination fields. Retrospective comparison of laser and filtered broadband sources suggests equivalent efficacy in topical PDT.[11] In the last few years, LED sources have shown considerable development, with improvements in design making these relatively inexpensive sources convenient for wide area irradiation and popular for patient use, e.g. the Aktilite 16 and 128 (Galderma) and the Omnilux (Photo Therapeutics Ltd, Altrincham, U.K.). These LED sources match the 630/635-nm activation peak of PpIX while excluding the extraneous wavelengths present in broadband sources, thus permitting shorter irradiation times. Biophysical calculations indicate that an LED source with peak emission of 631 ± 2 nm may have a deeper PDT action in tissue than a filtered halogen lamp of 560–740 nm emission, and hence LED may be more effective in treating the deeper parts of tumours.[12]

PpIX has its largest absorption peak in the blue region at 410 nm (Soret band), with smaller absorption peaks at 505, 540, 580 and 630 nm. Most light sources for PDT seek to utilize the 630-nm absorption peak in the red region, in order to improve tissue penetration. However, a blue fluorescent lamp (peak emission 417 nm) is routinely used in Levulan ALA-PDT of AK in the U.S.A. There are now several reports

that blue, green and red light can each be effective in topical PDT of AK, but the more deeply penetrating red light is superior when treating BD and BCC.[1]

A report has recently described the concept of ambulatory PDT to reduce hospital attendance for PDT.[13] In a pilot study of five patients with BD, PDT was performed with ALA and a portable LED device, where low irradiance light exposure took place over 100 min (ALA 4 h, 637 nm, 75 J cm^{-2}, 12 mW cm^{-2}). Pain was minimal in most, and four of five patients were in clinical remission after a median of 9 months. In contrast, Britton *et al.*[14] used a pulsed dye laser (PDL) for ALA-PDT in BD, with the aim of reducing irradiation time. Overlapping 7-mm spots were applied to cover the lesions (ALA 4 h, 585 nm, 10 J cm^{-2}, 22 mW cm^{-2}), achieving high response rates and shorter average exposure time (~450 ms), but the procedure required considerable time and skill on the part of the operator for larger lesions. There was also significant post-treatment morbidity including slow healing and scarring.

Recent studies have suggested that pulsed light therapy may be useful for treatment/adjunctive treatment in topical PDT of acne, AK and photorejuvenation (see later sections). However, a recent controlled investigative study, performed in healthy human skin *in vivo* following microdermabrasion and acetone scrub, showed that two pulsed light sources previously reported in PDT, the PDL and a broadband flashlamp filtered intense pulsed light (IPL), produced evidence of minimal activation of photosensitizer, with a dramatically smaller photodynamic reaction than seen with a conventional continuous wave broadband source.[15] The IPL and PDL sources deliver intense light in periods < 20 ms, which might suppress oxygen consumption.[16] Inadvertent ambient light exposure may have significantly contributed to the clinical effect. On the other hand, three studies have recently addressed the possibility of using ambient light for ALA-PDT of AK, with two reports of therapeutic benefit, but with a randomized ambient light-controlled study using Levulan ALA demonstrating no significant effect on lesion ablation.[15,17,18] A randomized right/left intrapatient comparison of conventional MAL-PDT delivered with an LED device vs. daylight (for 2·5 h) for the treatment of AK of face and scalp showed an equivalent reduction in AK and significantly less pain with daylight.[19] Although ambient light exposure might achieve a therapeutically effective dose in certain circumstances, it is unlikely to offer a consistent, practical and safe approach to the delivery of PDT.

Total effective light dose or fluence is proposed as a concept for optimizing the accuracy of light dosimetry in PDT, taking into account incident spectral irradiance, optical transmission through tissue and absorption by photosensitizer.[20] In practice, light dosimetry is described as the irradiance or fluence rate (mW cm^{-2}) at the skin surface and the total dose or fluence (J cm^{-2}) delivered to the surface, the latter being a product of irradiance and time of exposure.

Experimental evidence has suggested that lower fluence rates and fractionation of light exposure could improve lesional response by promotion of the photodynamic reaction.[21] A study of superficial BCC, illuminated with 45 J cm^{-2} at 4 h and repeated at 6 h with 633-nm laser light at 50 mW cm^{-2}, observed a complete response of 84% after a mean of 59 months.[22] More recent studies are presented in the individual indication sections later in this report. In brief, current data support superiority of the fractionation approach in BCC, although not in BD.[23,24]

Currently, a range of light sources, doses and irradiances continues to be used in ALA-PDT, whereas in MAL-PDT the standard procedure now typically involves an LED source. A range of continuous wave light sources is effective in topical PDT (*Strength of recommendation A, Quality of evidence* II-iii).

Protocols for delivery of photodynamic therapy

Optimization of PDT outcome requires consideration of mechanism of action and application of the most appropriate drug and light parameters. The photodynamic reaction is dependent on the presence of sufficient quantities of photosensitizer, activating light and oxygen. For utilization of this reaction, the prodrug/photosensitizer requires a high selectivity for the target vs. healthy tissue. Topically applied prodrugs are converted intracellularly to the active photosensitizer and exert direct effects on the target cells, while intravenous photosensitizers may exert a major effect on tumour vasculature, with consequent ischaemia of tumour tissue. Reactive oxygen species (ROS), principally singlet oxygen, released by the photodynamic reaction result in apoptosis of target cells, and necrosis is also reported. A vigorous inflammatory reaction usually occurs, followed by an immune response which may help eradicate residual tumour cells.[25]

In topical PDT, the first consideration is that the prodrug should be able to penetrate the skin and be delivered to the target tissue in sufficient quantities and at the required depth. As reported in the original guidelines,[1] co-application of the penetration enhancer dimethylsulphoxide and the iron chelator ethylenediamine tetraacetic acid sodium appeared to enhance the efficacy of ALA-PDT in nodular BCC, although no randomized comparison data are available. In a within-subject comparison of both healthy skin and matched skin malignancies treated with ALA-PDT alone or combined with the iron chelator desferrioxamine, significantly higher PpIX levels were seen after application of the combined agents to healthy tissue, but the lesional levels were very variable.[26] Glycolic acid may increase the tissue penetration of ALA.[27] Several papers now report the use of lesional surface preparation prior to application of prodrug;[28] this is generally a mild procedure involving the removal of surface crust or scale, producing little if any bleeding and not requiring local anaesthesia. Other investigators report perforation or even removal of the intact epithelium overlying nodular BCC; however, the impact of these procedures is unknown.[29] In a recent comparison study, each half of 16 lesions (superficial BCC or BD) was randomly assigned to surface preparation (gentle curettage or abrasion with a scalpel) or none, then treated with ALA-PDT. There

was no significant difference in the response of lesions in this small study.[30]

Topical ALA-PDT has been used with a variety of protocols, apart from its defined use in solution form with blue light in AK (Levulan ALA with blue-U), whereas PDT utilizing MAL is practised according to its licensed use, based on the findings of optimization studies.[3] In nodular BCC of up to 2 mm thickness, a 3-h application of 160 mg g^{-1} MAL showed the highest selectivity for tumour, and this time interval was confirmed in a recent study;[31] this procedure is licensed in the form of two treatments 1 week apart for BCC, with the aim of reaching deeper parts of the tumour at the second treatment. It is also licensed as a double treatment for BD, but in AK only one initial treatment is recommended, with nonresponders receiving a second treatment at 3 months (see AK section). In contrast to MAL, the drug–light interval applied in ALA-PDT varies widely.[1] Interestingly, whereas ALA has typically been applied for longer periods, there are now publications reporting its efficacy when applied for 3 h, as with MAL.[32] Also, while the Levulan ALA and blue-U system is licensed for a drug–light interval of 18–24 h, efficacy of this formulation when applied for 1–3 h in ALA-PDT is reported in AK and photodamage.[33] Further studies are required to optimize the drug–light interval in ALA-PDT.

The use of fluorescence spectroscopy and microscopy, to assess the time course and depth of tissue photosensitizer fluorescence, respectively, has previously been described[1] and these are applied primarily in research centres to explore methods for optimizing protocols. Illumination of a porphyrin-enriched tumour by a Wood's lamp [long wave ultraviolet (UV) A] leads to a typical brick-red fluorescence which can be utilized in detecting and delineating poorly defined tumours, and this principle can also be applied quantitatively with CCD camera systems coupled to digital imaging.[34]

The use of pulsed ultrasound to assess the depth of BCC prior to and following treatment has helped to predict treatment outcome, and could potentially be used in the future to assist decisions regarding treatment protocols.[35]

Topical photodynamic therapy in nonmelanoma skin cancer

Actinic keratoses

Previously reviewed open studies described clearance rates of 71–100% facial and scalp AKs, but a lower response of 44–73% AKs on acral sites, following a single treatment with PDT using nonlicensed ALA preparations.[1] During the past 5 years, nine randomized multicentre control/comparison studies ($n = 4$ ALA-PDT and $n = 5$ MAL-PDT), using licensed formulations, have been published for the treatment of facial and scalp AK.

The combined report of two such studies in 243 patients with multiple AKs stated that 75% or more lesions resolved in 77% of patients after one treatment with Levulan ALA-PDT (ALA 14–18 h, 417 ± 5 nm, 10 J cm^{-2}, 10 mW cm^{-2}).[36] A second treatment at 8 weeks increased this rate to 89% (vs. 13% in placebo) with a lesion response rate, at 12 weeks, of 91% (placebo 31%). Moderate-to-severe stinging or discomfort was reported by at least 90% of patients.

A randomized two-centre study compared broad-area topical Levulan ALA-PDT (ALA 1 h, blue light 417 ± 5 nm, 10 J cm^{-2}, 10 mW cm^{-2}) with topical 5-fluorouracil (5-FU) 0·5% cream applied for 4 weeks in 36 patients with multiple face/scalp AKs. No difference in efficacy was evident 4 weeks post-treatment, with 80% and 79% lesion clearance, respectively, although PDT delivered to a third group using a 595-nm PDL cleared only 50% of lesions.[37] Additional open studies of 'short-contact' (0·5–3 h application) Levulan ALA-PDT, with prior topical 5-FU[38] or without,[32,33,39–41] achieved lesion clearance rates of 69–98% after single sessions using blue, IPL or PDL sources. Comparison of 3 h with 14–18 h Levulan ALA application demonstrated equivalent efficacy of 90% at 8 months.[32] Nonfacial AKs were included in this study with overall lower response rates of 70% for the extremities and 65% for the trunk at 4 months.

Sustainability of the response of AKs to Levulan ALA-PDT was reported in a study of 110 patients each with multiple thin or moderate thickness AKs on their face or scalp.[42] Up to two treatments (20% ALA 14–18 h, 417 ± 5 nm, 10 J cm^{-2}, 10 mW cm^{-2}) achieved a peak target lesion clearance of 86% reducing to 78% at 12 months. The histologically confirmed recurrence rate at 12 months was 19%.

Three randomized comparison/control studies of MAL-PDT using the same protocol (MAL 3 h, 570–670 nm, 75 J cm^{-2}, 50–250 mW cm^{-2}) cleared 69% of predominantly thin and moderate thickness AKs of the face or scalp after a single treatment,[43] increasing to 89–91% where two treatments were performed 7 days apart.[44,45] In comparison, clearance rates of 68% and 75% were recorded for cryotherapy in two of these studies,[43,45] with placebo responses of 30–38%.[44,45] Significant superiority of cosmetic response was observed in both studies that compared PDT with cryotherapy.[43,45]

Using a narrowband red LED light source (634 ± 3 nm, 37 J cm^{-2}, 50 mW cm^{-2}), a randomized study compared single MAL-PDT (3-h application), repeated at 3 months if required, with routine initial double therapy 7 days apart.[46] The protocols were equally effective, clearing 92% and 87% of lesions, respectively, with a single treatment clearing 93% of thin lesions and 70% of moderate thickness AKs. This study led to the European licence for MAL-PDT in AK being revised in 2006 in most countries to recommend an initial single treatment, with repeat at 3 months if required.

A large randomized intra-individual study of 1501 face/scalp AKs in 119 patients compared MAL-PDT using the same LED and MAL dosing parameters as above, with double freeze-thaw cryotherapy, repeating treatments at 3 months if required.[47] After the initial cycle of treatments, PDT resulted in a significantly higher cure rate than cryotherapy (87% vs. 76%), but with equivalent outcome after all nonresponders were re-treated (89% vs. 86%). Overall subject preference (cosmesis, efficacy and skin discomfort) significantly favoured

PDT. A recent study comparing MAL-PDT with cryotherapy for AK on the extremities demonstrated inferior efficacy with PDT, with clearance of 78% of lesions at 6 months compared with 88% for cryotherapy.[48]

Topical PDT is an effective therapy for thin and moderate thickness AK, with superiority to cryotherapy depending on protocol. Efficacy is relatively poorer for acral lesions, but PDT may still offer therapeutic benefit. Cosmetic outcome following PDT for AK is superior to cryotherapy (*Strength of recommendation A, Quality of evidence* I).

Bowen's disease

Topical ALA-PDT clears, on average, 86–93% of lesions of BD following one or two treatments.[1] Three small randomized trials using nonlicensed ALA formulations and identical protocols demonstrated PDT to be equivalent to cryotherapy,[49] superior to topical 5-FU[50] and significantly more effective when delivered using narrowband red rather than green light.[51]

Several alternative protocols have been reported since the original guidelines. A small study observed a response of BD to ALA and violet light (8 h, 400–450 nm, 10–20 J cm^{-2}, 5·4–10·8 mW cm^{-2}) in all five evaluable patients, although with recurrence in one of five by 6 months.[52] The use of low-irradiance LED light sources applied to lesions to permit ambulatory PDT has been discussed above.[13] Fractionation of light during ALA-PDT for BD (20 J cm^{-2} then 80 J cm^{-2} at 4 and 6 h) has been compared with standard single illumination (75 J cm^{-2} at 4 h) and achieved equivalent response rates of 88% and 80%, respectively, at 12 months, suggesting no current advantage to split illumination.[24]

Topical MAL-PDT has recently been compared with clinician's choice of cryotherapy or 5-FU in a multicentre randomized controlled trial of 225 patients with 275 lesions (MAL 3 h, 570–670 nm, 75 J cm^{-2}, 70–200 mW cm^{-2}).[53] Three months after last treatment, clearance rates were similar following MAL-PDT (86%), cryotherapy (82%) and 5-FU (83%). PDT gave superior cosmetic results compared with cryotherapy and 5-FU (good or excellent in 94%, 66% and 76%, respectively). After 24 months of follow up, 68% of lesions remained clear following PDT, 60% after cryotherapy and 59% after 5-FU.[54]

Topical PDT has been reported in case reports to clear BD in unusual sites (nipple, subungual)[55–57] and where it arises in a setting of poor healing (lower leg, epidermolysis bullosa and radiation dermatitis).[58–60]Topical PDT can be effective in digital lesions, with four patients treated in one study clearing to give good cosmetic and functional results (one recurrence at 8 months).[61] Complete resolution of localized bowenoid papulosis in two patients followed ALA-PDT using 6–12 h application and a same-day fractionated illumination schedule.[62]

Topical ALA-PDT has been observed to offer therapeutic benefit in erythroplasia of Queyrat.[63,64] MAL-PDT cleared residual erythroplasia following Mohs surgery for penile SCC.[65] Paoli *et al.*[66] observed that PDT (ALA/MAL) to 10 patients with penile intraepithelial neoplasia resulted in clearance in seven patients, but later recurrence in four. There was sustained clearance in the remaining patients over 46 months, including clearance of human papillomavirus (HPV) DNA.

Topical PDT is an effective therapy for BD, with equivalence to cryotherapy and equivalence or superiority to topical 5-FU. Cosmetic outcome is superior to standard therapy. Topical PDT offers particular advantages for large/multiple patch disease and for lesions at poor healing sites (*Strength of recommendation A, Quality of evidence* I).

Squamous cell carcinoma

There remain limited data on the efficacy of topical PDT for primary cutaneous invasive SCC. Clearance rates for superficial lesions of 54–100% have been observed following ALA-PDT in series of five to 35 lesions, but with recurrence rates ranging from 0% to 69% (weighted average 30%) and reduced efficacy for the few nodular lesions treated.[1,67]

Topical ALA-PDT cleared an SCC in a hospitalized patient with xeroderma pigmentosum, but produced an enhanced phototoxic reaction lasting over 2 weeks despite the absence of UV radiation.[68] Caution is advised in this indication following the report of a 5-year-old patient with DeSanctis–Cacchione syndrome, a variant of xeroderma pigmentosum, where PDT using a systemic photosensitizer to multiple eyelid SCCs was followed by a rapid extension of tumours within the treatment field.[69]

The high efficacy of topical PDT for *in situ* SCC, and the efficacy figures reported particularly for superficial invasive lesions limited to papillary dermis, suggest that depth of therapeutic effect is the limiting factor for PDT in invasive SCC, with further study required. Current evidence supports the potential of topical PDT for superficial, microinvasive SCC, but in view of its metastatic potential, topical PDT cannot currently be recommended for the treatment of invasive SCC (*Strength of recommendation D, Quality of evidence* II-iii).

Basal cell carcinoma

Superficial BCCs were reported to respond well to ALA-PDT with a weighted clearance rate of 87% in one review of 12 studies, compared with 53% for nodular lesions.[70] Prior debulking curettage achieved a clearance rate for nodular BCC in one study of 92% compared with 0% in the control groups (curettage or PDT alone).[71] One randomized comparison of PDT (ALA 6 h, 635 nm, 60 J cm^{-2}, 80 mW cm^{-2}) vs. cryotherapy for mixed BCC showed no difference in efficacy over 1 year but superior cosmesis with PDT.[72] The original guidelines concluded PDT to be effective in superficial BCC, but that adjunctive therapy might be required to enhance efficacy for nodular BCC.[1] However, a recent study failed to show a significant advantage of curettage followed by PDT (ALA 6 h, 630 nm, 125 J cm^{-2}, 120 mW cm^{-2}, repeated at 3 months) compared with conventional surgery for nodular BCC up to 2 cm in diameter, with clearance rates of 72% and 100%, respectively, of treatment sites reviewed at 1 year.[73]

Further approaches taken in an attempt to increase the response of BCC, particularly nodular lesions, have been to use the more lipophilic methyl ester of ALA, MAL, and to use routine double PDT treatments. In a large retrospective report of MAL-PDT for BCC, where most lesions received a single treatment (MAL 3 or 24 h, 570–670 nm, 50–200 J cm^{-2}, 100–180 mW cm^{-2}) with nodular lesions receiving prior debulking curettage, an initial complete response was observed in 310 lesions, and 277 remained clear after 35 months, with a good or excellent cosmetic response in 98%.[74] The overall cure rate for the 350 superficial and nodular BCCs was 79%, an encouraging result particularly as the population included lesions failing previous treatments. To date there has been only one small randomized study directly comparing ALA-PDT with MAL-PDT in BCC (ALA and MAL 3 h, 600–730 nm, 75 J cm^{-2}, 100 mW cm^{-2}), with no difference in lesional response on histological analysis after 8 weeks, and residual tumour in six treatment sites in each study group.[9]

Fractionation of light may enhance the efficacy of topical PDT in BCC. In an open study of ALA-PDT, 86 superficial BCCs were illuminated with red light (ALA, 633 nm, 45 J cm^{-2}, 50 mW cm^{-2}) at 4 and 6 h, with initial clearing of 76 (88%) lesions and sustained clearance of 56 of 67 (84%) evaluable lesions at 59 months.[22] The same group subsequently undertook a randomized comparison trial of 505 superficial BCCs (ALA, 630-nm diode laser or 633-nm LED or broadband light 590–650 nm, 50 mW cm^{-2}), treated with either a single illumination of 75 J cm^{-2} or twofold illumination with 20 J cm^{-2} and 80 J cm^{-2} at 4 and 6 h.[23] Twelve months after treatment, ALA-PDT with single illumination cleared 89% of tumours, while fractionated PDT produced a significantly higher response rate of 97%.

Two prospective uncontrolled multicentre studies have subsequently reported on routine double MAL-PDT treatment of 'difficult to treat' BCC (superficial and nodular) including lesions occurring on the mid-face or ear locations, of large size, and recurring after other treatments. Lesion surface preparation involved gentle scraping of superficial lesions, while nodular lesions were prepared by removing any intact overlying epidermis ± some debulking. The protocol also allowed for a second cycle of MAL-PDT (two treatment sessions) in lesions showing partial response at 3 months. In the first study [MAL 3 h, 570–670 nm ($n = 106$) or 580–740 nm ($n = 2$), 75 J cm^{-2}, 50–200 mW cm^{-2}], 87% of 108 difficult to treat lesions showed complete lesion response at 3 months when assessed clinically, falling to 77% after histological review.[29] After 2 years, the lesion recurrence rate was 22%, with recurrence rate apparently increasing with lesion diameter, while 94% of patients showed a good or excellent cosmetic outcome. Similarly, a study of 95 patients with 148 BCC lesions showed that PDT (MAL 3 h, 570–670 nm, 75 J cm^{-2}, 50–200 mW cm^{-2}) achieved a histologically confirmed lesion complete response rate of 89% at 3 months while the estimated sustained lesion complete response rate at 2 years was 78%, at which time 84% of patients were judged to have a good or excellent cosmetic response.[75] Lesions in the H-zone and large lesions were noted to have lower sustained complete response rates.

Multicentre randomized studies have now been reported for MAL-PDT vs. standard treatment for BCC, with long-term (5 year) follow-up data becoming available. A randomized study compared double MAL-PDT with treatments 7 days apart (MAL 3 h, 570–670 nm, 75 J cm^{-2}, 50–200 mW cm^{-2}) with standard surgical excision, in 101 patients with small nodular BCC amenable to simple excision.[28] Lesions (24%) with a noncomplete response to PDT at 3 months were re-treated. Clinical complete response rates at 3 months did not differ significantly between groups, with 98% in those treated with surgery vs. 91% of lesions treated with MAL-PDT, and with total disease-free response rates at 12 months of 96% vs. 83%, respectively. A recent 5-year follow up of this study has revealed a significantly higher estimated sustained lesion response rate for surgery at 96% compared with 76% for MAL-PDT.[76] Over 5 years, 14% of lesions recurred after MAL-PDT vs. 4% for surgery, although no further recurrences with MAL-PDT were seen after the first 3 years. Cosmetic evaluation showed significantly better results for MAL-PDT, with 87% showing a good or excellent outcome at 5 years after PDT compared with 54% in the surgical group. These results imply that while surgery remains the gold standard for the treatment of nodular BCC, MAL-PDT is effective for treatment of these lesions and exhibits a more favourable cosmetic outcome.

A similar 5-year follow-up study has compared cryotherapy with PDT (MAL 3 h, 570–670 nm, 75 J cm^{-2}, 50–200 mW cm^{-2}) for the treatment of superficial BCC. The 3-month complete clinical response rates were similar for PDT (97% of 102 BCCs) and cryotherapy (95% of 98 lesions). Cosmetic outcome was superior following PDT, with an excellent or good outcome reported in 87% (PDT group) and 49% (cryotherapy). The estimated complete lesion response rate at 5 years was 75% in the MAL-PDT group vs. 74% in the cryotherapy group, with recurrence of 22% of lesions which had initially cleared following MAL-PDT, compared with 20% after cryotherapy.[77]

Topical MAL–PDT and ALA–PDT are effective treatments for superficial BCC (*Strength of recommendation A, Quality of evidence I*). Topical MAL–PDT is effective in nodular BCC, although with a lower efficacy than excision surgery, and may be considered in situations where surgery may be suboptimal (*Strength of recommendation B, Quality of evidence I*).

Cutaneous T-cell lymphoma

Several case reports[78,79] and case series successfully utilizing topical ALA-PDT and MAL-PDT for early stage localized cutaneous T-cell lymphoma (CTCL) have been published since the original guidelines, with multiple treatments usually required for clearance. One report of ALA-PDT used an incoherent red light source (ALA 5–6 h, 600–730 nm, 88–180 J cm^{-2}, 20–265 mW cm^{-2}) in 10 patients with mycosis fungoides (MF) (10 plaque lesions and two tumours) with a median number of two treatments (range 2–11 treatments).[80]

There was complete clinical clearance in seven of nine evaluable plaque lesions, but neither tumour responded. Complete remission is reported of four patients with CTCL IA–IIB treated with one to seven topical ALA-PDT treatments using an incoherent light source (ALA 6 h, 600–730 nm, 72–144 J cm^{-2}, 60–120 mW cm^{-2}).[81] These patients had varied histological types including two patients with MF, one CD30+ anaplastic large cell lymphoma and one CD8+ CTCL. Another report observed remission in four patients with unilesional MF and partial response in another following one to nine PDT treatments (MAL 3 h, 635 ± 18 nm, 37·5 J cm^{-2}, 86 mW cm^{-2}).[82]

Topical PDT using ALA (n = 2) and MAL (n = 1) has also achieved clinical and histological remission after one or two treatments in three patients with localized thin plaque cutaneous B-cell lymphoma, with clearance maintained over 8–24 months.[83]

The selective uptake of photosensitizers into lymphocytes, discussed in the original guidelines, offers an explanation for the potential of PDT in CTCL. Malignant T lymphocytes may be more susceptible than keratinocytes to PDT-induced lysis, as illustrated in a study using the novel photosensitizer silicon phthalocyanine.[84]

Topical PDT can elicit a response and has a potential role in the treatment of localized CTCL. Further studies of PDT for CTCL are required to define optimal treatment parameters (*Strength of recommendation C, Quality of evidence II-iii*).

Intraepithelial neoplasia of the vulva and anus

Limited data reviewed in the original guidelines suggested that topical ALA-PDT could be effective in the treatment of vulval intraepithelial neoplasia (VIN). Complete histological clearance of VIN grade III in 11 of 15 (73%) patients was achieved following PDT (ALA 2–3 h, 635 nm, 125 J cm^{-2}), with no difference in disease-free survival at 1 year compared with patients treated with laser ablation or surgery.[85] Multifocal disease was found to be a predictor of poor response to PDT. The same group also reported the histologically confirmed clearance of 57% of 22 patients with VIN II/III again following a single ALA-PDT treatment.[86] PDT was viewed as being as effective as conventional therapies, but with shorter healing times and absence of scarring. A significant post-treatment increase of cytotoxic T-cell infiltration in VIN lesions responding to ALA-PDT has been observed compared with non-responding VIN; and the presence of high-grade dysplasia and/or high-risk HPV is associated with a poor response to PDT.[87] A retrospective review of different modalities for VIN observed a 48% relapse rate following PDT, comparable with 42% following local excision and 40% treated by laser vaporization over 54 months.[88] Topical PDT has been used to treat intraepithelial neoplasia of the anus.[89] High recurrence rates, typical of tissue-preserving therapies for these indications, necessitate close follow up of patients and more detailed comparison studies are required. Drug application remains challenging for these intraepithelial neoplasias and facilitated delivery using bioadhesive patches or systemic photosensitizers is being explored.[90–92]

Topical PDT offers therapeutic benefit in VIN, but refinement of practical aspects of delivery and optimization of protocol are required (*Strength of recommendation C, Quality of evidence II-iii*).

Extramammary Paget's disease

In the original guidelines, evidence for the use of topical PDT as monotherapy for extramammary Paget's disease (EMPD) was lacking. A retrospective review identified five men with 16 EMPD lesions, 11 recurrent from standard therapies, who had received Levulan ALA-PDT and red light.[93] Six months after one treatment, eight lesions were clear, but three recurred after a further 3–4 months. Although recurrence is common with conventional therapies, the authors speculate that PDT using systemic photosensitizers might be more suitable for bulky disease. A further two cases of EMPD are reported of response to ALA-PDT, and seven patients with recurrent EMPD of the vulva were treated using MAL-PDT and red light, with clearance in four.[94,95] PDT with the ALA applied via a bioadhesive patch, followed by red light illumination, cleared vulval EMPD after four treatments, with histological confirmation.[96]

Topical PDT, although potentially effective in EMPD, is currently associated with high recurrence rates in the limited cases reported (*Strength of recommendation C, Quality of evidence III*).

Photodynamic therapy for skin cancer prophylaxis

Repeated ALA-PDT treatments can delay the appearance of UV-induced skin cancer in mice.[97] Although an increased mortality and a greater incidence of large tumours in the PDT-treated mice were observed in the initial study, more recent studies have not concurred with this finding, with both systemic (intraperitoneal) and topical ALA-PDT in mice showing delayed appearance of UV-induced tumours in mice but no increased mortality or incidence of large tumours,[98,99] and similar findings reported for topical MAL-PDT in UV-treated mice.[100] In the study by Liu *et al.*,[99] a delay in large tumour appearance was observed in mice whether ALA-PDT was started concurrent with or at the end of UV exposure. Recently, a study of topical MAL-PDT in *PTCH* heterozygous mice exposed to UV radiation has shown significant prevention of development of microscopic BCC.[101] At 28 weeks, 19 BCCs were found in nine of 20 mice exposed to UV only whereas there were no BCCs in 15 mice additionally exposed to PDT.

The mechanism by which PDT delays the onset of UV-induced skin cancer is unknown. It is known that PpIX preferentially accumulates in neoplastic cells, and light activation may induce both necrosis and apoptosis of these cells.[102] Topical PDT may cause selective destruction of keratinocytes bearing mutated p53 induced by UV exposure.[100] Alternatively or additionally PDT may be inducing an immune response against neoplastic cells and acting as a biological response

modifier.[103,104] Observed reduction in expected AK in clinical trials in organ transplant recipients (OTRs) (see section below) may in large part be due to the treatment of subclinical lesions, and evidence of a primary preventive effect of topical PDT in humans is lacking. Hence, current evidence indicates that topical PDT has the potential to provide a preventive role although further evidence is required to clarify its mechanism of action (*Strength of recommendation C, Quality of evidence IV*).

Photodynamic therapy in organ transplant recipients

OTRs are at a significantly increased risk of skin cancer.[105,106] The risk relates to the duration and degree of immunosuppression, HPV infection, and exposure to UV radiation. These tumours tend to be multiple, occurring within areas of dysplastic 'field change', and often behave in a more aggressive manner. PDT offers the potential of treating large target sites which may include multiple tumours, AK and preclinical skin cancers. In addition, it can provide a more satisfactory cosmetic outcome and, more importantly, may provide a means of preventing the development of skin cancer.

Clinical response rates for OTRs (n = 20) and immunocompetent (n = 20) individuals were compared in an open prospective trial of PDT (ALA 5 h, 600–730 nm, 75 J cm^{-2}, 80 mW cm^{-2}) for AK and BD.[107] Clinical response in both groups was similar at 4 weeks, with 86% and 94%, respectively. However, by 48 weeks the response rate in the OTRs had reduced to 48% compared with 72% in the immunocompetent patients. The reduced effectiveness of topical PDT in OTRs compared with immunocompetent individuals lends support to the importance of the role of immune response factors in its mechanism of action. The same group reported, in a randomized controlled trial, an observed clearance of AK in 13 of 17 OTRs at 16 weeks in areas treated by MAL-PDT (3 h, 600–730 nm, 75 J cm^{-2}, 80 mW cm^{-2}).[108] Another group reported complete remission of 24 tumours (75%) in five OTRs with 32 facial tumours (21 BCC, eight AK, one keratoacanthoma and two SCC), following PDT (ALA 3–5 h, 635 nm, 120 J cm^{-2}, 100 mW cm^{-2}).[109] Two tumours, both SCC, were refractory to PDT.

A recent open intrapatient randomized study of 27 renal OTRs reported a significant delay in development of new lesions at sites treated with PDT (MAL 3 h, 570–670 nm, 75 J cm^{-2}) compared with control sites (9·6 vs. 6·8 months).[110] By 12 months 62% of treated areas were free from new lesions compared with 35% in control areas. However, no significant difference in the occurrence of SCC was observed in another study of PDT (ALA 4 h, 400–450 nm, 5·5–6 J cm^{-2}) vs. no treatment after 2 years follow up in 40 OTRs.[111] A less pronounced increase in keratotic skin lesions in the PDT-treated sites was apparent but was not significant. Of note, in this latter study violet was used rather than red light and keratotic lesions were not pretreated by curettage.

A small randomized intrapatient comparison study compared PDT (MAL 3 h, 633 ± 15 nm, 75 J cm^{-2}, 80 mW cm^{-2}) with topical 5-FU for treatment of epidermal dysplasia in OTRs.[112] PDT (two treatments 7 days apart) was shown to be more effective and cosmetically acceptable than 5-FU (applied twice daily for 3 weeks) at 6-month follow up, PDT clearing eight of nine lesion areas, compared with only one of nine areas treated by 5-FU (lesional area reduction: PDT 100%, 5-FU 79%).

Current evidence suggests that topical PDT, although showing lower efficacy than in immunocompetent individuals, may provide a useful therapy for epidermal dysplasias in OTRs (*Strength of recommendation B, Quality of evidence I*).

Topical photodynamic therapy for infectious and inflammatory dermatoses

Acne and related conditions

PDT may promote improvement in acne via antibacterial activity against *Propionibacterium acnes*, selective damage to sebaceous glands, reduction in follicular obstruction by keratinocyte shedding and via secondary host responses.[113,114] *Propionibacterium acnes* naturally produces small amounts of certain porphyrins, especially coproporphyrin III, with topical ALA application promoting its accumulation.[115]

A randomized controlled trial of PDT (Levulan ALA 3 h, 550–700 nm, 150 J cm^{-2}) for acne on the back of 22 subjects demonstrated a significant reduction in inflammatory acne for 10 weeks after a single treatment and for at least 20 weeks after four treatments.[113] Sebum excretion and bacterial porphyrin fluorescence were both decreased, and sebaceous gland size was still reduced at 20 weeks after PDT, but treatment induced skin exfoliation and hyperpigmentation. A further randomized intraindividual controlled study of ALA-PDT (3 h, 635 nm, 15 J cm^{-2}, 25 mW cm^{-2}) for acne on the back demonstrated a significant reduction in inflammatory lesion counts after three weekly treatments, but without reductions in *P. acnes* numbers or sebum excretion. Despite the less intense regimen, postinflammatory pigmentation was observed in all patients for 1–3 months.[114]

Several open studies report a clinical benefit of topical ALA-PDT (both ALA and Levulan ALA) in facial acne using a range of application times from 0·25 to 4 h and a variety of light sources including blue light and IPL.[116] Protocol variations, some including preparatory peels, with small patient numbers and short follow-up periods, limit interpretation of these studies, with the extent of accumulation of photoactive porphyrins after very short applications yet to be determined. One intrapatient controlled study observed a 42% reduction in the inflamed lesion count 6 months following a single session of PDT (ALA 4 h, 630 ± 3 nm, 18 J cm^{-2}, 30 mW cm^{-2}) in mild-to-moderate facial acne, compared with 15% reduction in the untreated side.[117] In an open controlled study of 15 patients with a wide range of severity of facial acne, PDT (Levulan ALA 45 min, 595 nm, 7 J cm^{-2}) achieved a lesional clearance rate of 77% at 6 months (32% for the light-only controls) after a mean of 2·9 treatments (range 1–6).[118] A

small study of Levulan ALA applied to half the face of 13 patients with acne followed by illumination using an IPL source to both sides resulted in improved response on the PDT treatment side, sustained at 8 weeks.[119] In a further pilot study of IPL-delivered ALA-PDT in 14 patients, lesion counts decreased by 88% after three treatments, compared with 67% following IPL alone.[120] A recent split-face comparison of ALA-PDT using blue light with blue light alone in 20 Asian patients with moderate-to-severe acne showed a greater reduction in inflamed lesions on the PDT side (71% vs. 57% at 16 weeks after four weekly sessions), but the difference was not significant.[121]

Three randomized studies have recently been reported of MAL-PDT in acne. In a randomized, controlled, investigator-blinded study of 36 patients with moderate-to-severe disease, PDT was performed with gentle lesion curettage prior to initial treatment (MAL 3 h, 635 nm, 37 J cm^{-2}, 34 mW cm^{-2}), and repeated 2 weeks later. At 3 months, a significant 69% reduction in inflammatory lesions was observed, with no change in the control group, and no reduction in noninflammatory counts.[122] All patients experienced moderate to severe pain during treatment and developed severe erythema, pustular eruptions and epithelial exfoliation. A randomized split-face comparison study of 15 patients, by the same group, of ALA- and MAL-PDT (3 h, single treatment, dosimetry as above) achieved a 59% reduction in inflammatory lesions after 3 months in both groups, but with moderate-to-severe pain and pustular reactions, more severe in the ALA-PDT-treated areas.[8] A further randomized, placebo-controlled, split-face study of PDT (MAL 3 h, 635 nm, 37 J cm^{-2}) treated 30 patients with moderate-to-severe facial acne, with PDT repeated after 2 weeks.[123] Nodular and cystic lesions were prepared using a small cannula to facilitate cream penetration. A greater reduction in inflammatory lesions was observed at 12 weeks following PDT (54% vs. 20%). A recent blinded randomized study of PDT using IPL in Asian skin, where MAL was applied for only 45 min, failed to show significant improvement of moderate inflammatory acne compared with control.[124] A small randomized split-face trial compared long-pulsed dye laser alone with the use of the laser in MAL-PDT in 15 patients. There was greater reduction in inflammatory lesions on sites receiving PDT-enhanced laser therapy (80% vs. 67% at week 12).[125] A reduction in inflammatory lesion counts (on average by 58%) has also been observed in a case series of seven patients with chronic recalcitrant folliculitis arising in areas of acne-prone skin following a single treatment of MAL-PDT.[126]

Several case reports and case series report a therapeutic benefit of topical PDT using ALA, Levulan ALA and MAL in sebaceous hyperplasia[127–130] as well as for the treatment of a sebaceous naevus although treatment of the latter was combined with curettage.[131] Further studies are required to determine longevity of effect. ALA-PDT to four patients with Fordyce spots, heterotopic sebaceous glands, produced only mild improvement after two to nine treatments.[132] One case series observed improvement in hidradenitis suppurativa, although another series failed to confirm this, with deterioration in two patients following PDT.[133,134]

Although topical PDT can improve inflammatory acne on the face and back, optimization of protocols, to sustain response while minimizing adverse effects, is awaited (*Strength of recommendation B, Quality of evidence I*).

Viral warts

Clearance rates of 56–100% were noted in the case series and comparison trials of refractory warts and verrucas reported in the original guidelines.[1] In a subsequent controlled trial, PDT (ALA 5 h, 400–700 nm, 50 J cm^{-2}, 50 mW cm^{-2}) in 67 patients with plantar warts cleared 75% of warts (48 of 64) compared with a 22% reduction in untreated warts.[135] In another study, PDT (ALA 4–8 h, 580–720 nm, 100 mW cm^{-2}) in 31 patients with 48 plantar warts cleared 42 warts (88%), with better clearance seen in younger patients, larger warts and with longer treatment times.[136]

A study compared the treatment of verrucae by PDT using either a PDL or LED source, with the use of PDL alone (ALA 3 h, PDL at 595 nm and 20 J cm^{-2}, LED at 635 nm and 50 J cm^{-2}), with clearance rates of 100% (mean 1·96 treatments), 96% (mean 2·54 treatments) and 81% (mean 3·34 treatments), respectively.[137] Pretreatment of patients with plantar warts with 3% azone prior to ALA-PDT resulted in clearance in 67% and 100% of mosaic and myrmeci (single deep painful warts) subtypes, respectively, while clearance after ALA-PDT alone was 37·5% and 70%, respectively.[138] Success of topical ALA-PDT in a patient with multiple facial plane warts has been reported, following two treatments with ALA applied for 6 h and illumination with a metal halide lamp (peaks at 630 and 700 nm).[139] Complete clearance of periungual hand warts in 18 of 20 patients (36 of 40 warts) was achieved in a pilot study of ALA-PDT after a mean of 4·5 fortnightly treatments.[140]

Recent studies continue to support the potential of topical PDT in viral warts, particularly plantar warts, but it appears a relatively painful therapy option, with outcomes dependent on adequate paring and the use of a keratolytic agent pre-PDT (*Strength of recommendation B, Quality of evidence I*).

Genital warts

A clearance rate of 66% in 16 patients with vulval and vaginal condylomata was achieved following PDT (ALA 2–4 h, 635 nm, 80–125 J cm^{-2}, 88 ± 17 mW cm^{-2}).[86] In a further case series of 12 male patients with condylomata acuminata treated with PDT (ALA 6–11 h, 400–800 nm, 70–100 J cm^{-2}, 70 mW cm^{-2}) an overall cure rate of 73% was achieved.[141] In addition, this study showed, using *in vivo* fluorescence kinetics, that the optimal time for illumination varied from 6 to 11 h. However, in a large open study of 164 patients, between one and four treatments with PDT (ALA 3 h, 630 nm, 100 J cm^{-2}, 100 mW cm^{-2}) cleared 95% of lesions, with only 5% recurring after 6–24 months.[142] Disappointing

results of PDT (ALA 5 h, 630 nm, 37 J cm^{-2}, 68 mW cm^{-2}) were seen in nine men with genital condylomata unresponsive to conventional therapies, with clearance only in three, after four treatments.[143] A recent randomized study compared ALA-PDT (ALA 3 h, 633 nm, 100 J cm^{-2}, 100 mW cm^{-2}) with conventional CO_2 laser in 65 patients with condylomata acuminata.[144] One treatment cleared 95% and 100% of lesions, respectively, with persisting lesions clearing following repeat PDT. A lower recurrence rate followed PDT (6% vs. 19%) and the authors concluded that PDT was a simpler, more effective therapy. Topical PDT may be considered as a treatment option for patients with genital warts (*Strength of recommendation B, Quality of evidence I*).

Cutaneous leishmaniasis

Recently, topical PDT has been reported to be effective in the treatment of cutaneous leishmaniasis, caused by *Leishmania major*. The challenge in treating this condition is to reduce lesion size in order to promote healing with minimal scarring, while also seeking to eradicate the amastigotes.

In a series of 11 patients (32 lesions), one or two weekly treatments with topical ALA-PDT, using broadband red light, rendered smears amastigote negative. Re-examination after 3–6 months revealed 31 of 32 lesions to remain amastigote negative with no relapses over 6 months and an average reduction in lesion size of 67%.[145] In a further series of five patients with ALA-PDT repeated weekly for 4 weeks, clearance of all lesions occurred, with eradication of amastigotes (by smear and culture), good cosmetic outcome, and no relapse over 4 months.[146]

A comparison of topical MAL-PDT, using red light, with a conventional therapy, daily topical paromomycin, in 10 lesions in the same patient, revealed that after a total of 28 PDT treatments, all five PDT-treated lesions and two of five paromomycin-treated lesions had healed and were leishmania free by histology, although cultures were not performed.[147] A recent case report found clearance of unilesional disease with MAL-PDT using red light after only three treatments.[148]

In a randomized investigator-blinded trial of 57 patients (95 lesions) receiving weekly ALA-PDT with red light, twice-daily topical paromomycin or placebo, each over 4 weeks, lesion clearance at 8 weeks was seen in 94%, 41% and 13%, respectively.[149] Parasitological cure, by smear, was demonstrated in 100%, 65% and 20%, respectively.

A recent *in vitro* and *in vivo* mechanistic study concluded that response of cutaneous leishmaniasis to PDT is likely to be due to nonspecific tissue destruction accompanied by a depopulation of macrophages rather than direct killing of parasites, although a previous study did show *in vitro* selective destruction of amastigotes in macrophages following exposure to porphyrins.[150,151]

Current evidence suggests that topical PDT is effective in clearing lesions of cutaneous leishmaniasis although further studies with culture confirmation of amastigote clearance are required (*Strength of recommendation B, Quality of evidence I*).

Psoriasis

A small study of four patients with psoriasis comparing topical PDT (ALA 4 h, 630 nm, 10 J cm^{-2}, 120 mW cm^{-2}) and narrowband UVB therapy showed the superiority of the latter.[152] Treatment with PDT was poorly tolerated by patients because of pain and resulted in early termination of the trial. A report of eight patients with psoriasis treated with ALA-PDT (ALA 4–5 h, 630 nm, 10–30 J cm^{-2}, 35–315 mW cm^{-2}) showed significant improvement of plaques but treatment was again limited by a high frequency of discomfort and pain.[153] This study also showed that PDT induced dermal neovascularization in the treated psoriatic plaques – the mechanism of this is unknown. A randomized, observer-blinded study of PDT (ALA 4–6 h, 600–740 nm, 5–20 J cm^{-2}, 60 mW cm^{-2}) for 21 patients with psoriasis showed disappointing results.[154] Complete clearance was found in only eight and substantial improvement in four of 63 plaques.

Recently, a prospective randomized, double-blind phase I/II intrapatient comparison study of 12 patients with psoriasis treated by topical PDT (ALA 4–6 h, 600–740 nm, 20 J cm^{-2}, 60 mW cm^{-2}) has also shown limited mean improvement of 37·5%, 45·6% and 51·2% in the 0·1%, 1% and 5% ALA-treated groups, respectively.[155] Part of this improvement was related to the effects of prior use of salicylic acid. In addition, treatment was frequently interrupted by severe pain.

A single case of recalcitrant palmoplantar pustular psoriasis refractory to both acitretin and methotrexate has been reported showing significant benefit from topical ALA-PDT using a diode laser.[156] The same group reported marked improvement in two patients with intractable palmoplantar pustulosis and mild change in a third, following ALA-PDT with the diode laser, but seven to 10 weekly treatments were required.[157]

Overall, current evidence, combined with studies reviewed in our previous guidelines, does not support the use of topical ALA-PDT as a practical therapy for psoriasis (*Strength of recommendation D, Quality of evidence I*).

Photodynamic photorejuvenation

Chronic actinic damage, or photoageing, clinically comprises wrinkling, rough elastotic skin, dyschromia, lentigines, and telangiectases.[158] IPL (500–1200 nm) has been applied with the aim of reversing the features of photoageing. As AKs frequently coexist with other features of photoageing, there has been recent interest in exploring the potential merits of firstly combining the ALA with IPL (ALA-IPL) and secondly of using standard PDT, for treatment of both chronic photodamage and AK.

In a case series of 17 subjects, 33 of 38 (87%) AKs resolved after two sessions of ALA-IPL, but the ALA was applied only to the sites of the AK and therefore the effects of ALA-IPL on photodamage were not explored.[159] In a further case series of 17 subjects it was reported that ALA-IPL was effective in both AK and photodamage.[41] Levulan ALA was applied to the entire

face for 1 h, with subsequent illumination from an IPL source (560-nm filter), clearing 68% of AKs and achieving improvement in telangiectasia, pigmentary irregularities and skin texture. The treatment was reported to be well tolerated. PDT using blue light has also been studied (ALA 1, 2 or 3 h, 400–410 nm, 10 J cm^{-2}, 10 mW cm^{-2}), in a case series of 18 patients with a combination of nonhypertrophic facial AKs and mild to moderate diffuse facial photodamage.[33] A clearance rate for AKs of 85–96% was observed after 1 month, with no difference between ALA incubation times. Regarding photodamage, modest but significant improvements were seen in the Griffiths score,[160] fine wrinkling and degree of sallowness, with borderline improvement of mottled pigmentation. All patients reported discomfort during the procedure, with moderately severe phototoxic reactions observed on day 1 in all patients.

In a split-face study, all 20 subjects with a moderate or higher degree of photoageing received a course of five full-face treatments with IPL (515–1200 nm, 23–26 J cm^{-2}), but with ALA applied as adjunctive treatment for 0·5–1 h to a randomly assigned hemiface before the first three IPL treatments.[161] A significantly greater improvement was reported for the ALA-treated side 1 month after the final (IPL) treatment, with respect to global score for photoageing, mottled pigmentation, and fine lines. The authors stressed the importance of good photoprotective measures, including physical sun blocks, in the 48 h following treatment, and felt that this may have contributed significantly to the high tolerability of the procedure.

A further split-face study compared ALA-IPL with IPL alone, given three times at 1-monthly intervals in 13 subjects.[162] The ALA-pretreated side reportedly showed enhanced improvement of fine lines, skin roughness, mottled hyperpigmentation and telangiectases, compared with the side treated with IPL alone, although it is not clear whether randomization was performed and no statistical analysis is presented.

In a small randomized split-face study of PDT (MAL 1 and 3 h, 630 nm, 37 J cm^{-2}) in 10 patients with moderate photodamage, the authors noted an improvement in skin quality and fine wrinkling, although details on methodology and again, statistical analysis, are not provided.[163]

Interest is clearly gathering in this area, although at present there is a need for well-designed randomized, controlled, adequately powered studies with a longer follow up and ideally histological confirmation of clinical findings. The relative roles of PDT and IPL as treatment/adjunctive treatment are anticipated to undergo further exploration. Standard topical PDT (continuous wave light source) and ALA-IPL appear effective in photorejuvenation (*Strength of recommendation B, Quality of evidence II-iii*).

Other indications

Topical ALA-PDT has been reported to be effective in the treatment of localized scleroderma in five patients, with the same group demonstrating induction of the collagen-degrading matrix metalloproteinase (MMP)-1 and MMP-3 by fibroblasts following PDT.[164,165] In addition, interleukin-1 released by keratinocytes following PDT triggers MMP production in dermal fibroblasts in a paracrine manner.[166] Other photosensitizers used for PDT may be more effective in modifying collagen metabolism.[167]

Case series and individual reports describe the potential of topical PDT in a variety of other indications[168–194](Table 1). In addition to the limited evidence, several reports detail pain and inflammatory responses that potentially limit the practicality of using this modality outwith the setting of disease unresponsive to conventional therapies. However, it is possible that optimization of protocols could broaden the indication for topical PDT in inflammatory and infectious dermatoses.

Adverse effects

Acute

The most common and troublesome acute adverse event of topical PDT is the burning or stinging pain that occurs during light exposure, and may continue postexposure in a minority. Pain is restricted to the illuminated area and may reflect nerve stimulation and/or tissue damage by ROS, possibly aggravated by hyperthermia.[1] Treatment of psoriasis and viral warts in particular is frequently limited by pain.[1,155] Pain appears more intense in large area lesions, with AK, BD and BCC covering an area of > 130 mm^2 significantly more painful to treat.[195] The latter study also found a positive association of pain intensity with AK, lesions located on the head, and in the male sex, although these factors could not be dissociated. A further study of 94 patients, all with AK, found a clear dose–response relationship for lesion size and intensity of pain, but no significant difference between genders.[196] A large interindividual variation in pain experienced was noted in both studies, with approximately 20% of patients experiencing severe pain.[195,196]

The above studies were performed with the prodrug ALA. As ALA but not MAL is transported by γ-aminobutyric acid carriers, it has been speculated that MAL might provoke less nerve fibre stimulation and subsequent pain.[197] In a double-blind randomized study in tape-stripped healthy skin of the forearm, pain was found to be significantly higher in the ALA- than the MAL-treated sites, both during and immediately after PDT (ALA and MAL 3 h, 570–670 nm, 70 J cm^{-2}, 90 mW cm^{-2}).[198] The ALA-treated skin showed a higher PpIX fluorescence peak than MAL-treated skin, and a greater decrease in peak PpIX fluorescence was seen during illumination in ALA-PDT. No correlation was found between pain and peak PpIX fluorescence, nor absolute decrease in peak PpIX fluorescence; however, the high intersubject variability could potentially obscure any relationship in this small subject group. In a recent comparison study of pain during MAL-PDT for acne and AK, pain was shown to be greater with more intense PpIX fluorescence and also with higher fluence rate.[199] Two comparison studies have observed that MAL-PDT was less painful than ALA-PDT for the treatment of scalp AK, although

Table 1 Topical photodynamic therapy (PDT) beyond nonmelanoma skin cancer: applications suggested on the basis of case reports and case series

Condition	Study	No. patients	Treatments	PDT	Outcome
Actinic cheilitis[168–170]	CS + CS + CS	3 + 3 + 15	ALA-PDT: 1–3 MAL-PDT: 2 MAL-PDT: 2	ALA, broadband (n = 3) MAL, red (n = 3) MAL, red (n = 15)	All sites cleared, good cosmesis, no recurrence 6–12 months. In large series, complete clearance in 47%, partial clearance in 47%
Disseminated superficial actinic porokeratoses[171,172]	CS + CR	3 + 1	2 (CS), 2 (CR)	ALA, red (n = 3) MAL, red (n = 1)	CS: Initial response in one of three only at 4 weeks CR: Marked improvement, no recurrence at 1 year
Localized pagetoid reticulosis[173]	CR	1	3	ALA, red	Histological clearance, no recurrence at 1 year
Nephrogenic fibrosing dermopathy[174]	CR	1	2	MAL, red	Normal texture by 4 weeks, no recurrence at 1 year
Hailey–Hailey disease[175]	CS	2	2	ALA, red	Histological clearance, no recurrences at 19–25 months
Darier disease[176,177]	CS + CR	6 + 1	1	ALA, red (n = 6) ALA, blue (n = 1)	Four cleared/improved, one exacerbated
Lichen planus (penile)[178]	CR	1	2	ALA, red	Complete clearance, no recurrence at 6 months
Vulval lichen sclerosus[179]	CS	12	1–3	ALA, red	Improved pruritus (10 of 12) for mean of 6 months
Extragenital lichen sclerosus[180]	CR	1	3	ALA, red	Complete clearance, no recurrence at 2 years
Sarcoidosis[181]	CR	1	22	3% ALA gel + DMSO, red	Histological clearance, no recurrence at 18 months
Necrobiosis lipoidica[182]	CR	1	6	MAL, red	Histological clearance, no recurrence at 2 years
Granulation in Goltz syndrome[183]	CR	1	1	MAL, red	Followed curettage, clearance for 8 months
Rosacea[184,185]	CS + CR	4 + 1	1 (CS), 6 (CR)	MAL + red (n = 4) Levulan ALA + PDT at 595 nm (n = 1)	CS: Response in three, sustained in one to 9 months CR: Excellent response, only 1 month review
Perioral dermatitis[186]	SFC	21	4	Levulan ALA, blue	92% lesions clear (vs. 81% on clindamycin); seven of 21 did not complete due to photosensitivity reactions
Radiodermatitis[187]	CS	5	2–8	ALA, red (+ near infrared)	Remission in two, partial clearing in three
Venous leg ulcer[188]	CR	1	8	ALA, red	Significant improvement, clearance of MRSA
Molluscum contagiosum[189,190]	CS + CR	6 + 1	3–5 (CS), 4 (CR)	Levulan ALA, blue	Reduced lesion counts (all patients HIV positive)
Epidermodysplasia verruciformis[191]	CR	1	1	ALA, red	Histological clearance, but HPV not eradicated, new lesions at 1 year
Erythrasma[192]	CS	13	1	Endogenous porphyrins, red	Clearance in three, 30% reduction in other cases
Interdigital mycoses[193]	CS	9	1–4	ALA, red	Clinical and mycological clearance in six, but recurrence in four by 1 month
Mycobacterium marinum[194]	CR	1	3	MAL, red	Clearance of lesion unresponsive to light alone, no recurrence at 7 months

CS, case series; CR, case report; SFC, split-face comparison (nonrandomized); ALA, 5-aminolaevulinic acid; MAL, methyl aminolaevulinate; DMSO, dimethyl sulphoxide; MRSA, methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; HPV, human papillomavirus.

ALA was applied for 6 and 5 h, respectively, compared with the shorter application time of 3 h for MAL.[10,200] Two recently reported small studies comparing MAL- and ALA-PDT in the indications of nodular BCC and acne, with application of each prodrug for 3 h, found no significant difference between the agents in pain experienced during treatment, although in the acne study the ALA-PDT side was significantly more painful 24 h after treatment.[8,9] Degree of pain also appears related to intensity of light delivery; fractionated light doses increase tolerance of the procedure, and may at the same time increase cure rates.[201] A recent split-face randomized study compared variable pulse light (VPL) with LED for MAL-PDT of face and scalp AK (MAL 3 h; VPL 610–950 nm, 80 J cm^{-2} vs. LED 635 ± 3 nm, 37 J cm^{-2}, 50 mW cm^{-2}). Pain score was significantly lower on the VPL side (visual analogue score 4·3 vs. 6·4), with similar, although relatively low, remission rates at 3 months (47% for VPL vs. 57% for LED) for both light sources.[202]

A range of techniques has been used in an attempt to reduce PDT-related pain, including local anaesthesia and cooling the skin with fans or sprayed water.[1] No significant difference was seen between patients receiving topical anaesthesia with amethocaine or control in a randomized double-blind study in 42 patients with superficial NMSC (ALA 3–5 h, 630 nm, 125 J cm^{-2}, 20–125 mW cm^{-2}).[203] Due to high intersubject variability in pain experienced, and the differing diagnoses and sites, it is conceivable that a significant effect could have been obscured. However, the effect of a topical mixture of lignocaine and prilocaine (EMLA®; AstraZeneca, Luton, U.K.) vs. control was also studied in 14 men with extensive scalp AK and again no significant alleviation of pain with the use of topical anaesthesia was observed.[204]

Cold air analgesia may be effective in topical PDT.[205] Two matched superficial skin cancers were treated either with or without cold air analgesia (−35 °C) at the time of irradiation. While no significant difference was seen in pain score at the first session, the score was significantly lower during the second treatment session of the cold air-treated lesion. The investigators also found that level of skin erythema was reduced after treatment. It is conceivable that the profound cooling induced by this device could result in a significant vasoconstriction, theoretically making less oxygen available for the photodynamic reaction.

Other than pain, topical PDT has a low morbidity, and few significant acute adverse effects occur. An acute inflammatory response is observed, sometimes followed by erosion and crust formation. Complete healing usually occurs within 2 weeks but is reported occasionally to take up to 6 weeks.[1] A small minority of patients shows a heightened acute inflammatory response, during or immediately after PDT, typically when wide areas of the face/scalp are treated. Recent investigations have shown that the erythema and oedema seen immediately postirradiation are attributable to a dose-related urticarial response mediated by histamine, and that this occurs to some degree in all subjects.[206] Caution has been advised in treating large skin fields by PDT in case of pronounced phototoxic reaction, with the option to consider initial small-area PDT prior to large-field exposure.[207] The skin inflammation induced by PDT might contribute to its therapeutic effect, acting as an optimizing event for the development of specific antitumour immunity and long-term suppression of tumour growth after PDT.[21] Interestingly, it was found in a study of ALA-PDT for AK that pretreatment lesional erythema was significantly related to both PDT-induced pain and the cure rate.[196] The pretreatment erythema is likely to reflect degree of vasodilatation and inflammation in the lesions, and may indicate the amount of oxygen locally available. Further clinical studies are clearly required, to determine whether interventions that reduce pretreatment erythema or the PDT-induced inflammatory response may impact adversely on therapeutic effect.

Pain is a common feature during light exposure in PDT, but topical PDT is overall a well-tolerated treatment modality with a low rate of serious acute adverse events (*Strength of recommendation A, Quality of evidence I*).

Application of topical anaesthetics is of limited use for pain relief during light exposure of AK (*Strength of recommendation D, Quality of evidence II-i*).

Chronic

The incidence of scarring associated with topical PDT is very low and is reflected in the good or excellent cosmetic outcome widely reported, including in the randomized comparison trials of PDT in NMSC indications reported above and in the original guidelines.[1] *In vivo* studies of the effect of haematoporphyrin-mediated PDT compared with hyperthermia on mouse skin compliance have found the former not to produce a fibrotic response.[208] The levels of collagen measured *in vitro* are elevated in modalities associated with scarring *in vivo* (e.g. ionizing radiation, hyperthermia and bleomycin) but not after exposure to haematoporphyrin ester-mediated PDT.[209]

Postinflammatory hypopigmentation or hyperpigmentation can occur following PDT.[1] Studies on healthy skin showed that hyperpigmentation following PDT is dependent on ALA dose, occurs after 48–72 h and increases during the 2 weeks following treatment.[26,210] Hyperpigmentation of psoriatic lesions following PDT appears to be common. Mild to moderate pigmentation was seen in all PDT-treated lesions in a study of 21 patients with psoriasis and in seven of eight patients in a further study.[153,154] However, pigmentary disturbance appears only occasionally to be more than a minor complication of skin tumour PDT. Pigmentary change was observed in only 1% of lesions (mild/moderate scarring: 0·8%) from a centre reporting on PDT for 762 patients with NMSC.[211] Hair loss is a potential side-effect of PDT as concomitant sensitization of the pilosebaceous unit takes place.[212] Permanent localized hair loss following PDT is uncommon but has occurred more frequently after treatment of BCC rather than BD, presumably determined by the extent of involvement of pilosebaceous units by the primary disease.[213]

Carcinogenicity

As PDT does not induce covalent modifications of DNA, treatment-related carcinogenesis is expected to be low or absent compared with UV therapy.[214] In addition, porphyrin-like molecules also possess antioxidant and antimutagenic properties.[215] PDT has the potential of promoting genotoxic effects from the generation of ROS, but with effects limited to the vicinity of their site of generation, and ROS liberated by ALA- and MAL-PDT mediate their effects in the mitochondria as opposed to the nucleus.[216] Recent research has shown that PDT induces low levels of p53 and generated ROS do not induce DNA damage via p53 phosphorylation pathways as seen with PUVA.[217] PDT does not induce cyclobutane pyrimidine dimers or (6–4) photoproducts, as induced by UV radiation: these are DNA lesions that are associated with characteristic p53 mutations at dipyrimidine sites in NMSC.[218]

Two cases of skin cancer possibly related to PDT have previously been reported in the original guidelines.[64,219] One was a melanoma arising in the scalp of a patient receiving PDT for AK, the other an SCC arising in an area of erythroplasia of Queyrat treated by PDT. In the past 5 years, only one further lesion possibly induced by topical PDT has been reported, in a patient who developed a keratoacanthoma after ALA-PDT for treatment of AK.[220]

Topical PDT has a low risk of carcinogenicity and reported cases of skin cancer occurring in relation to this therapy are rare (*Strength of recommendation A, Quality of evidence* II-iii).

Safety aspects of topical photodynamic therapy

Contraindications to PDT include a history of porphyria and allergy/photoallergy to active ingredients of the applied photosensitizer.[221–223] Blue light can pose a hazard to the retina, potentially causing irreversible damage to the photosensitive neurotransmitters in the macula.[1] However, most PDT is carried out using red light which is not phototoxic to the retina. Nevertheless, the wearing of goggles for both patient and staff is recommended to limit the transmission of high-intensity light and to avoid discomfort and disturbance of colour perception.

Following topical PDT, localized photosensitivity can remain for up to 48 h, ALA degrading with a half-life of about 24 h, and MAL-induced PpIX clearing from normal skin within 24–48 h.[224,225]

Photodynamic therapy: cost assessment

The original guidelines provided a detailed cost-comparison of ALA-PDT with standard therapy derived from two studies of BD.[1] Estimated costs for ALA-PDT were comparable with cryotherapy and topical 5-FU when morbidity costs were included, but reflected the use of a nonlicensed ALA preparation and light sources no longer in routine use. A cost-minimization study of six treatments commonly used for BD in the U.K. National Health Service concluded that ALA-PDT was the most expensive option for treating a single lesion, but considered average costs for three light sources now rarely used, including laser, making extrapolation difficult to current practice of PDT.[226] The cost of topical PDT will be influenced by clinic set-up, opportunities for safe multiple use of the same package for more than one lesion/patient, nurse/technician- vs. doctor-led therapy, use of relatively low-cost LED sources, etc. A discrete choice survey of members of the general public in Australia demonstrated that preference for avoidance of scarring was considered to be more important even than lesion response, with a willingness to pay more for MAL-PDT over simple excision for BCC.[227]

A recent detailed economic evaluation of topical MAL-PDT, based on multicentre comparison trials for AK,[45] superficial and nodular BCC,[28,77] calculated the cost per full responder, defined as clearance of all lesions in a patient and an excellent cosmetic outcome. The authors concluded that PDT is a cost-effective intervention in AK when compared with cryotherapy over 1 year, and better value for money than excision in BCC when compared over 5 years (to allow time for recurrences).[228] This industry-sponsored study took into account response rates, possible recurrence and cosmesis as well as estimating the costs of managing nonresponse, recurrence and nonexcellent cosmetic outcome, and represents the most detailed consideration, to date, of the relative cost of PDT when a value on cosmetic outcome benefit is included.

Novel methods of delivering topical PDT could improve its cost-effectiveness. The cost-effectiveness of delivering topical PDT in a community setting was demonstrated in a small randomized study using a portable PDT light source, with therapy delivered by a nurse, permitting a more convenient service for typically elderly patients presenting with BD and BCC.[229] Ambulatory PDT could minimize hospital resources as well as offer treatment at/closer to home using portable LED devices.[13] Further studies are required to update cost-effectiveness analysis for topical PDT as currently used in the U.K. National Health Service, with particular consideration to its use in multiple and/or large lesions/field treatments.

Overview

These updated guidelines provide strong evidence confirming the high efficacy of topical PDT in AK, BD and superficial BCC. Randomized comparison studies also support the efficacy of topical PDT, following lesion preparation, in thin nodular BCC, with recurrence rates over 5 years recently published. Licensed products and convenient light sources with short irradiation times are now available for topical PDT in NMSC.

The response of OTRs to PDT appears reduced compared with immunocompetent controls, but this modality may still be useful for the treatment and possible prevention of NMSC in this challenging situation. Current evidence demonstrates reductions in anticipated lesion numbers following PDT; the relative contribution of primary prevention of *de-novo* lesions and treatment of preclinical lesions requires study. The lack of

additional studies of PDT in SCC cautions practitioners not to use topical PDT where invasive malignancy is suspected. Small patient numbers of individual reports continue to limit the evidence for PDT in localized CTCL, although available data are encouraging.

Since the original guidelines a large number of additional applications for topical PDT has been described in the literature (Table 1). It appears that efficacy as well as greater patient tolerance of PDT can be achieved in infective and inflammatory indications through lower dose, less intense treatment regimens, although multiple treatments are usually required. A variety of protocols, including several randomized studies, results in clinical response of acne to PDT, but a narrow therapeutic window may exist between clinical and phototoxic responses, potentially limiting patient tolerance. Further study data indicate disappointing outcomes of PDT for psoriasis. In contrast, several reports now describe the clearance of cutaneous leishmaniasis lesions by topical PDT, an interesting novel indication.

During the past 5 years, considerable interest has been shown in the potential of PDT to promote photorejuvenation with observed improvements of fine lines, skin roughness and mottled hyperpigmentation. Further well-designed studies are required.

Topical PDT is well tolerated, while treatment-associated pain remains problematic for certain indications. To date, the use of topical anaesthesia appears ineffective, and alternative therapies, including cold air analgesia, offer scope for pain reduction when required. Reports of possible secondary skin malignancy remain very low, and high-quality cosmesis following PDT is consistently observed.

Tools for guideline users

Presented in this update:

1 Summary of the evidence for PDT in its principal approved and emerging indications.

2 A tabular summary of possible applications of topical PDT where evidence is currently restricted to case reports and series (Table 1).

3 A summary of the main recommendations from this comprehensive update (Table 2).

4 Suggestions for audit.

Possible audit points

1 Initial clearance rates of AK, BD and superficial BCC at 3 months after last treatment of at least 75% lesions.

2 Sustained clearance rates of AK, BD and superficial BCC at 12 months after last treatment of at least 75% lesions.

3 Recurrence rates at 24 months post-treatment in BD and at 24–36 months in superficial BCC of no more than 20% lesions.

4 Demonstration of an effective protocol for pain management with severe pain in < 10% of patients treated for individual BD/BCC lesions by standard technique.

Table 2 Clinical indications for topical photodynamic therapy in dermatology: recommendations and evidence assessment

Strength of recommendation	Quality of evidence	Indication
A	I	Thin and moderate thickness actinic keratoses
		Bowen's disease
		Superficial basal cell carcinoma
B	I	Thin nodular basal cell carcinoma
		Epidermal dysplasias in organ transplant recipients
		Inflammatory acne on the face and back
		Viral warts, particularly plantar warts
		Genital warts
		Cutaneous leishmaniasis
B	II-iii	Photorejuvenation
C	II-iii	Localized cutaneous T-cell lymphoma
		Vaginal intraepithelial neoplasia
C	III	Extramammary Paget's disease
C	IV	Skin cancer prevention
D	I	Psoriasis
D	II-iii	Invasive squamous cell carcinoma

5 Cosmetic outcome at 1 year – demonstrate satisfaction (good-excellent) with cosmesis in a minimum of 80% of patients.

References

1 Morton CA, Brown SB, Collins S *et al.* Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2002; **146**:552–67.

2 National Institute for Health and Clinical Excellence. *IPG155. Photodynamic Therapy for Non-Melanoma Skin Tumours (Including Premalignant and Primary Non-Metastatic Skin Lesions)*. 2006. Available at: http://www.nice.org.uk/page.aspx?o=IPG155guidance (last accessed 29 August 2008).

3 Peng Q, Soler AM, Warloe T *et al.* Selective distribution of porphyrins in thick basal cell carcinoma after topical application of methyl 5-aminolevulinate. *J Photochem Photobiol B* 2001; **62**:140–5.

4 Peng Q, Warloe T, Moan J *et al.* Distribution of 5-aminolevulinic acid-induced porphyrins in noduloulcerative basal cell carcinoma. *Photochem Photobiol* 1995; **62**:906–13.

5 Martin A, Tope WD, Grevelink JM *et al.* Lack of selectivity of protoporphyrin IX fluorescence for basal cell carcinoma after topical application of 5-aminolevulinic acid: implications for photodynamic treatment. *Arch Dermatol* 1995; **287**:665–74.

6 Ahmadi S, McCarron PA, Donnelly RF *et al.* Evaluation of the penetration of 5-aminolevulinic acid through basal cell carcinoma: a pilot study. *Exp Dermatol* 2004; **13**:445–51.

7 Fritsch C, Homey B, Stahl W *et al.* Preferential relative porphyrin enrichment in solar keratoses upon topical application of delta-aminolevulinic acid methylester. *Photochem Photobiol* 1998; **68**:218–21.

8 Wiegell S, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006; **54**:647–51.

9 Kuijpers D, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol* 2006; **5**:642–5.

10 Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol* 2007; **157**:87–91.

11 Clark C, Bryden A, Dawe R *et al.* Topical 5-aminolaevulinic acid photodynamic therapy for cutaneous lesions: outcome and comparison of light sources. *Photodermatol Photoimmunol Photomed* 2003; **19**:134–41.

12 Juzeniene A, Juzenas P, Ma LW *et al.* Effectiveness of different light sources for 5-aminolevulinic acid photodynamic therapy. *Lasers Med Sci* 2004; **19**:139–49.

13 Moseley H, Allen JW, Ibbotson S *et al.* Ambulatory photodynamic therapy: a new concept in delivering photodynamic therapy. *Br J Dermatol* 2006; **154**:747–50.

14 Britton JER, Goulden V, Stables G *et al.* Investigation of the use of the pulsed dye laser in the treatment of Bowen's disease using 5-aminolaevulinic acid phototherapy. *Br J Dermatol* 2005; **153**:780–4.

15 Strasswimmer J, Grande DJ. Do pulsed lasers produce an effective photodynamic therapy response? *Lasers Surg Med* 2006; **38**:22–5.

16 Kawauchi S, Morimoto Y, Sato S *et al.* Differences between cytotoxicity in photodynamic therapy using a pulsed laser and a continuous wave laser: study of oxygen consumption and photobleaching. *Lasers Med Sci* 2004; **18**:179–83.

17 Marcus SL, Houlihan A, Lundahl S, Ferdon ME. Does ambient light contribute to the therapeutic effects of topical photodynamic therapy (PDT) using aminolevulinic acid (ALA)? *Lasers Surg Med* 2007; **39**:201–2.

18 Batchelor RJ, Stables GI, Stringer MR. Successful treatment of scalp actinic keratoses with photodynamic therapy using ambient light. *Br J Dermatol* 2007; **156**:779–81.

19 Wiegell SR, Haedersdal M, Philipsen PA *et al.* Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. *Br J Dermatol* 2008; **158**:740–6.

20 Moseley H. Total effective fluence: a useful concept in photodynamic therapy. *Lasers Med Sci* 1996; **11**:139–43.

21 Henderson B, Gollnick SO, Snyder JW *et al.* Choice of oxygen-conserving treatment regimen determines the inflammatory response and outcome of photodynamic therapy of tumours. *Cancer Res* 2004; **64**:2120–6.

22 Star WM, van't Veen AJ, Robinson DJ *et al.* Topical 5-aminolevulinic acid mediated photodynamic therapy of superficial basal cell carcinoma using two light fractions with a two-hour interval: long-term follow-up. *Acta Derm Venereol (Stockh)* 2006; **86**:412–7.

23 de Haas ER, Kruijt B, Sterenborg HJ *et al.* Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. *J Invest Dermatol* 2006; **126**:2679–86.

24 de Haas ER, Sterenborg HJ, Neumann HA, Robinson DJ. Response of Bowen disease to ALA-PDT using a single and a 2-fold illumination scheme. *Arch Dermatol* 2007; **143**:264–5.

25 Castano A, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. *Nat Rev Cancer* 2006; **6**:535–45.

26 Choudry K, Brooke RC, Farrar W, Rhodes LE. The effect of an iron chelating agent on protoporphyrin IX levels and phototoxicity in topical 5-aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 2003; **149**:124–30.

27 Ziolkowski P, Osiecka BJ, Oremek G *et al.* Enhancement of photodynamic therapy by use of aminolevulinic acid/glycolic acid drug mixture. *J Exp Ther Oncol* 2004; **4**:121–9.

28 Rhodes LE, de Rie M, Enström Y *et al.* Photodynamic therapy using topical methyl aminolevulinate vs. surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol* 2004; **140**:17–23.

29 Horn M, Wolf P, Wulf HC *et al.* Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *Br J Dermatol* 2003; **149**:1242–9.

30 Moseley H, Brancaleon L, Lesar AE *et al.* Does surface preparation alter ALA uptake in superficial non-melanoma skin cancer *in vivo*? *Photodermatol Photoimmunol Photomed* 2008; **24**:72–5.

31 Angell-Petersen E, Sørenson R, Warloe T *et al.* Porphyrin formation in actinic keratosis and basal cell carcinoma after topical application of methyl 5-aminolevulinate. *J Invest Dermatol* 2006; **126**:265–71.

32 Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. *Arch Dermatol* 2003; **139**:1313–20.

33 Touma D, Yaar M, Whitehead S *et al.* A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol* 2004; **140**:33–40.

34 Fritsch C, Lang K, Schulte KW *et al.* Fluorescence diagnosis and photodynamic therapy in dermatology: an overview. In: *Photodynamic Therapy* (Patrice T, ed.). Cambridge: Royal Society of Chemistry, 2003; 177–212.

35 Moore J, Allan E. Pulsed ultrasound measurements of depth and regression of basal cell carcinomas after photodynamic therapy: relationship to probability of 1-year local control. *Br J Dermatol* 2003; **149**:1035–40.

36 Piacquadio DJ, Chen DM, Farber HF *et al.* Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. *Arch Dermatol* 2004; **140**:41–6.

37 Smith S, Piacquadio D, Morhenn V *et al.* Short incubation PDT versus 5-FU in treating actinic keratoses. *J Drugs Dermatol* 2003; **2**:629–35.

38 Gilbert DJ. Treatment of actinic keratoses with sequential combination of 5-fluorouracil and photodynamic therapy. *J Drugs Dermatol* 2005; **4**:161–3.

39 Goldman M, Atkin D. ALA/PDT in the treatment of actinic keratosis: spot versus confluent therapy. *J Cosmet Laser Ther* 2003; **5**:107–10.

40 Gold MH. Intense pulsed light therapy for photorejuvenation enhanced with 20% aminolevulinic acid photodynamic therapy. *J Lasers Med Surg* 2003; **15** (Suppl.):47.

41 Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. *J Drugs Dermatol* 2004; **3** (Suppl.):S36–9.

42 Tschen EH, Wong DS, Pariser DM *et al.* The Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using

aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; **155**:1262–9.
43 Szeimies RM, Karrer S, Radakovic-Fijan S *et al.* Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; **47**:258–62.
44 Pariser DM, Lowe NJ, Stewart DM *et al.* Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol* 2003; **48**:227–32.
45 Freeman M, Vinciullo C, Francis D *et al.* A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix®) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatolog Treat* 2003; **14**:99–106.
46 Tarstedt M, Rosdahl I, Berne B *et al.* A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix®)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol (Stockh)* 2005; **85**:424–8.
47 Morton CA, Campbell S, Gupta G *et al.* Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; **155**:1029–36.
48 Kaufmann R, Spelman L, Weightman W *et al.* Multicentre intraindividual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. *Br J Dermatol* 2008; **158**:994–9.
49 Morton CA, Whitehurst C, Moseley H *et al.* Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *Br J Dermatol* 1996; **135**:766–71.
50 Salim A, Leman JA, McColl JH *et al.* Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol* 2003; **148**:539–43.
51 Morton CA, Whitehurst C, Moore JV, MacKie RM. Comparison of red and green light in the treatment of Bowen's disease by photodynamic therapy. *Br J Dermatol* 2000; **143**:767–72.
52 Dijkstra AT, Majoie IM, van Dongen JW *et al.* Photodynamic therapy with violet light and topical 6-aminolaevulinic acid in the treatment of actinic keratosis, Bowen's disease and basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2001; **15**:550–4.
53 Morton CA, Horn M, Leman J *et al.* Comparison of topical methyl aminolevulinate 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.
54 Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; **156**:793–801.
55 Brookes PT, Jhawar S, Hinton CP *et al.* Bowen's disease of the nipple – a new method of treatment. *Breast* 2005; **14**:65–7.
56 Tan B, Sinclair R, Foley P. Photodynamic therapy for subungual Bowen's disease. *Australas J Dermatol* 2004; **45**:172–4.
57 Usmani N, Stables GI, Telfer NR, Stringer MR. Subungual Bowen's disease treated by topical aminolevulinic acid-photodynamic therapy. *J Am Acad Dermatol* 2005; **53**:S273–6.
58 Ball SB, Dawber RPR. Treatment of cutaneous Bowen's disease with particular emphasis on the problem of lower leg lesions. *Australas J Dermatol* 1998; **39**:63–70.
59 Souza CS, Felicio LB, Bentley MV *et al.* Topical photodynamic therapy for Bowen's disease of the digit in epidermolysis bullosa. *Br J Dermatol* 2005; **153**:672–4.
60 Guillen C, Sanmartin O, Escudero A *et al.* Photodynamic therapy for *in situ* squamous cell carcinoma on chronic radiation dermatitis after photosensitization with 5-aminolaevulinic acid. *J Eur Acad Dermatol Venereol* 2000; **14**:298–300.
61 Wong TW, Sheu HM, Lee JY, Fletcher RJ. Photodynamic therapy for Bowen's disease (squamous cell carcinoma *in situ*) of the digit. *Dermatol Surg* 2001; **27**:452–6.
62 Yang CH, Lee JC, Chen CH *et al.* Photodynamic therapy for bowenoid papulosis using a novel incoherent light-emitting diode device. *Br J Dermatol* 2003; **149**:1297–9.
63 Stables GI, Stringer MR, Robinson DJ, Ash DV. Erythroplasia of Queyrat treated by topical aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 1999; **140**:514–17.
64 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.
65 Lee MR, Ryman W. Erythroplasia of Queyrat treated with topical methyl aminolevulinate photodynamic therapy. *Australas J Dermatol* 2005; **46**:196–8.
66 Paoli J, Ternesten Bratel A, Lowhagen G-B *et al.* Penile intraepithelial neoplasia: results of photodynamic therapy. *Acta Derm Venereol (Stockh)* 2006; **86**:418–21.
67 Wolf P, Rieger E, Kerl H. An alternative treatment modality for solar keratoses, superficial squamous cell carcinomas and basal cell carcinomas? *J Am Acad Dermatol* 1993; **28**:17–21.
68 Wolf P, Kerl H. Photodynamic therapy in patient with xeroderma pigmentosum. *Lancet* 1991; **337**:1613–14.
69 Procianoy F, Cruz A, Baccega A *et al.* Aggravation of eyelid and conjunctival malignancies following photodynamic therapy in DeSanctis–Cacchione syndrome. *Ophthal Plast Reconstr Surg* 2006; **22**:498–9.
70 Peng Q, Warloe T, Berg K *et al.* 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. *Cancer* 1997; **79**:2282–308.
71 Thissen MR, Schroeter CA, Neumann HA. Photodynamic therapy with delta-aminolaevulinic acid for nodular basal cell carcinomas using a prior debulking technique. *Br J Dermatol* 2000; **142**:338–9.
72 Wang I, Bendsoe N, Klinteberg CA *et al.* Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol* 2001; **144**:832–40.
73 Berroeta L, Clark C, Dawe RS *et al.* A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma. *Br J Dermatol* 2007; **157**:401–3.
74 Soler AM, Warloe T, Berner A, Giercksky KE. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *Br J Dermatol* 2001; **145**:467–71.
75 Vinciullo C, Elliott T, Francis D *et al.* Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; **152**:765–72.
76 Rhodes LE, de Rie MA, Leifsdottir R *et al.* Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; **143**:1131–6.
77 Basset-Séguin N, Ibbotson SH, Emtestam L *et al.* Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol* 2008; **18**:547–53.
78 Leman JA, Dick DC, Morton CA. Topical 5-ALA photodynamic therapy for the treatment of cutaneous T-cell lymphoma. *Clin Exp Dermatol* 2002; **27**:516–18.

79 Paech V, Lorenzen T, Stoehr A *et al.* Remission of cutaneous mycosis fungoides after topical 5-ALA sensitisation and photodynamic therapy in a patient with advanced HIV-infection. *Eur J Med Res* 2002; **7**:477–9.
80 Edström DW, Porwit A, Ros AM. Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: clinical and histological response. *Acta Derm Venereol* (Stockh) 2001; **81**:184–8.
81 Coors EA, von den Driesch P. Topical photodynamic therapy for patients with therapy-resistant lesions of cutaneous T cell lymphoma. *J Am Acad Dermatol* 2004; **50**:363–7.
82 Zane C, Venturini M, Sala R, Calzavara-Pinton P. Photodynamic therapy with methyl aminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed* 2006; **22**:254–8.
83 Mori M, Campolmi P, Mavilia L *et al.* Topical photodynamic therapy for primary cutaneous B-cell lymphoma: a pilot study. *J Am Acad Dermatol* 2006; **54**:524–6.
84 Garcia-Zuazaga J, Cooper K, Baron ED. Photodynamic therapy in dermatology: current concepts in the treatment of skin cancer. *Expert Rev Anticancer Ther* 2005; **5**:791–800.
85 Fehr MK, Hornung R, Schwarz VA *et al.* Photodynamic therapy of vulvar intraepithelial neoplasia III using topically applied 5-aminolevulinic acid. *Gynecol Oncol* 2001; **80**:62–6.
86 Fehr MK, Hornung R, Degen A *et al.* Photodynamic therapy of vulvar and vaginal condyloma and intraepithelial neoplasia using topically applied 5-aminolevulinic acid. *Lasers Surg Med* 2002; **30**:273–9.
87 Abdel-Hady E-S, Martin-Hirsch P, Duggan-Keen M *et al.* Immunological and viral factors associated with the response of vulval intraepithelial neoplasia to photodynamic therapy. *Cancer Res* 2001; **61**:192–6.
88 Hillemanns P, Wang X, Staehle S *et al.* Evaluation of different treatment modalities for vulvar intraepithelial neoplasia (VIN): CO_2 laser vaporization, photodynamic therapy, excision and vulvectomy. *Gynecol Oncol* 2006; **100**:271–5.
89 Hamdan KA, Tait IS, Nadeau V *et al.* Treatment of grade III anal intraepithelial neoplasia with PDT. *Dis Colon Rectum* 2003; **46**:1555–9.
90 McCarron PA, Ma LW, Juzenas P *et al.* Facilitated delivery of ALA to inaccessible regions via bioadhesive patch systems. *J Environ Pathol Toxicol Oncol* 2006; **25**:389–402.
91 Webber J, Fromm D. PDT for carcinoma *in situ* of the anus. *Arch Surg* 2004; **139**:259–61.
92 Campbell SM, Gould DJ, Salter L *et al.* Photodynamic therapy using *meta*-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; **151**:1076–80.
93 Shieh S, Dee AS, Cheney RT *et al.* Photodynamic therapy for the treatment of extramammary Paget's disease. *Br J Dermatol* 2002; **146**:1000–5.
94 Mikasa K, Watanabe D, Kondo C *et al.* 5-Aminolevulinic acid-based photodynamic therapy for the treatment of two patients with extramammary Paget's disease. *J Dermatol* 2005; **32**:97–101.
95 Raspagliesi F, Fontanelli R, Rossi G *et al.* Photodynamic therapy using a methyl ester of 5-aminolevulinic acid in recurrent Paget's disease of the vulva: a pilot study. *Gynecol Oncol* 2006; **103**:581–6.
96 Zawislak AA, McCarron PA, McCluggage WG *et al.* Successful photodynamic therapy of vulval Paget's disease using a novel patch-based delivery system containing 5-aminolevulinic acid. *Br J Obstet Gynaecol* 2004; **111**:1143–5.
97 Stender IM, Bech-Thomsen N, Poulsen T, Wulf HC. Photodynamic therapy with topical delta-aminolevulinic acid delays UV photocarcinogenesis in hairless mice. *Photochem Photobiol* 1997; **66**:493–6.
98 Sharfaei S, Viau G, Lui H *et al.* Systemic photodynamic therapy with aminolaevulinic acid delays the appearance of ultraviolet-induced skin tumours in mice. *Br J Dermatol* 2001; **144**:1207–14.
99 Liu Y, Viau G, Bissonnette R. Multiple large-surface photodynamic therapy sessions with topical or systemic aminolevulinic acid and blue light in UV-exposed hairless mice. *J Cutan Med Surg* 2004; **8**:131–9.
100 Sharfaei S, Juzenas P, Moan J, Bissonnette R. Weekly topical application of methyl aminolevulinate followed by light exposure delays the appearance of UV-induced skin tumours in mice. *Arch Dermatol Res* 2002; **294**:237–42.
101 Caty V, Liu Y, Viau G, Bissonnette R. Multiple large surface photodynamic therapy sessions with topical methyl aminolaevulinate in *PTCH* heterozygous mice. *Br J Dermatol* 2006; **154**:740–2.
102 Noodt BB, Berg K, Stokke T *et al.* Apoptosis and necrosis induced with light and 5-aminolaevulinic acid-derived protoporphyrin IX. *Br J Cancer* 1996; **74**:22–9.
103 Korbelik M, Dougherty GJ. Photodynamic therapy-mediated immune response against subcutaneous mouse tumours. *Cancer Res* 1999; **59**:1941–6.
104 Oseroff A. PDT as a cytotoxic agent and biological response modifier: implications for cancer prevention and treatment in immunosuppressed and immunocompetent patients. *J Invest Dermatol* 2006; **126**:542–4.
105 Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol* 2002; **47**:1–17.
106 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**:1881–91.
107 Dragieva G, Hafner J, Dummer R *et al.* Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation* 2004; **77**:115–21.
108 Dragieva G, Prinz BM, Hafner J *et al.* A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol* 2004; **151**:196–200.
109 Schleier P, Hyckel P, Berndt A *et al.* Photodynamic therapy of virus-associated epithelial tumours of the face in organ transplant recipients. *J Cancer Res Clin Oncol* 2004; **130**:279–84.
110 Wulf HC, Pavel S, Stender I, Bakker-Wensveen CAHB. Topical photodynamic therapy for prevention of new skin lesions in renal transplant recipients. *Acta Derm Venereol* (Stockh) 2006; **86**:25–8.
111 de Graaf YGL, Kennedy C, Wolterbeek R *et al.* Photodynamic therapy does not prevent cutaneous squamous-cell carcinoma in organ-transplant recipients: results of a randomized-controlled trial. *J Invest Dermatol* 2006; **126**:569–74.
112 Perrett CM, McGregor JM, Warwick J *et al.* Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007; **156**:320–8.
113 Hongcharu W, Taylor CR, Chang Y *et al.* Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol* 2000; **115**:183–92.
114 Pollock B, Turner D, Stringer MR *et al.* Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. *Br J Dermatol* 2004; **151**:616–22.

115 Ramstad S, Futsaether CM, Johnsson A. Porphyrin sensitization and intracellular calcium changes in the prokaryote, *Propionibacterium acnes*. *J Photochem Photobiol B* 1997; **40**:141–8.
116 Nester MS, Gold MH, Kauvar ANB *et al.* The use of photodynamic therapy in dermatology: results of a consensus conference. *J Drugs Dermatol* 2006; **5**:140–54.
117 Hong SB, Lee MH. Topical aminolevulinic acid-photodynamic therapy for the treatment of acne vulgaris. *Photodermatol Photoimmunol Photomed* 2005; **21**:322–5.
118 Alexiades-Armenakas M. Long-pulsed dye laser-mediated photodynamic therapy combined with topical therapy for mild to severe comedonal, inflammatory, or cystic acne. *J Drugs Dermatol* 2006; **5**:45–55.
119 Santos MA, Belo VG, Santos G. Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone in the treatment of acne vulgaris: comparative study. *Dermatol Surg* 2005; **31**:910–15.
120 Rojanamatin J, Choawawanich P. Treatment of inflammatory facial acne vulgaris with intense pulsed light and short contact of topical 5-aminolevulinic acid: a pilot study. *Dermatol Surg* 2006; **32**:991–6.
121 Akaraphanth R, Kananawanitchkul W, Gritiyarangsan P. Efficacy of ALA-PDT vs. blue light in the treatment of acne. *Photodermatol Photoimmunol Photomed* 2007; **23**:186–90.
122 Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol* 2006; **154**:969–76.
123 Hörfelt C, Funk J, Frohm-Nilsson M *et al.* Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol* 2006; **155**:608–13.
124 Yeung CK, Shek SY, Bjerring P *et al.* A comparative study of intense pulse light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. *Lasers Surg Med* 2007; **39**:1–6.
125 Haedersdal M, Togsverd-Bo K, Wiegell SR, Wulf HC. Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: a randomized controlled trial. *J Am Acad Dermatol* 2008; **58**:387–94.
126 Horn M, Wolf P. Topical methyl aminolevulinate photodynamic therapy for the treatment of folliculitis. *Photodermatol Photoimmunol Photomed* 2007; **23**:145–7.
127 Horio T, Horio O, Miyauchi-Hashimoto H *et al.* Photodynamic therapy of sebaceous hyperplasia with topical 5-aminolaevulinic acid and slide projector. *Br J Dermatol* 2003; **148**:1274–6.
128 Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. *J Drugs Dermatol* 2003; **2**:501–4.
129 Gold MH, Bradshaw VL, Boring MM *et al.* Treatment of sebaceous gland hyperplasia by photodynamic therapy with 5-aminolevulinic acid and a blue light source or intense pulsed light source. *J Drugs Dermatol* 2004; **3** (Suppl. 6):S6–9.
130 Perrett CM, McGregor J, Barlow RJ *et al.* Topical photodynamic therapy with methyl aminolevulinate to treat sebaceous hyperplasia in an organ transplant recipient. *Arch Dermatol* 2006; **142**:781–2.
131 Dierickx CC, Goldenhersh M, Dwyer P *et al.* Photodynamic therapy for nevus sebaceus with topical delta-aminolevulinic acid. *Arch Dermatol* 1999; **135**:637–40.
132 Kim YJ, Kang HY, Lee E-S, Kim YC. Treatment of Fordyce spots with 5-aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 2007; **156**:399–400.
133 Gold MH, Bridges NM, Bradshaw VL, Boring M. ALA-PDT and blue light therapy for hidradenitis suppurativa. *J Drugs Dermatol* 2004; **3**:S32–5.
134 Strauss RM, Pollock B, Stables GI *et al.* Photodynamic therapy using aminolaevulinic acid does not lead to clinical improvement in hidradenitis suppurativa. *Br J Dermatol* 2005; **152**:803–4.
135 Fabbrocini G, Di Costanzo MP, Riccardo AM *et al.* Photodynamic therapy with topical delta-aminolaevulinic acid for the treatment of plantar warts. *J Photochem Photobiol B* 2001; **61**:30–4.
136 Schroeter CA, Pleunis J, van Nispen tot Pannerden C *et al.* Photodynamic therapy: new treatment for therapy-resistant plantar warts. *Dermatol Surg* 2005; **31**:71–5.
137 Smucler R, Jatsová E. Comparative study of aminolevulinic acid photodynamic therapy plus pulsed dye laser versus pulsed dye laser alone in treatment of viral warts. *Photomed Laser Surg* 2005; **31**:51–3.
138 Ziolkowski P, Osiecka BJ, Siewinski M *et al.* Pretreatment of plantar warts with azone enhances the effect of 5-aminolevulinic acid photodynamic therapy. *J Environ Pathol Toxicol Oncol* 2006; **25**:403–10.
139 Mizuki D, Kaneko T, Hanada K. Successful treatment of topical photodynamic therapy using 5-aminolaevulinic acid for plane warts. *Br J Dermatol* 2003; **149**:1087–8.
140 Schroeter CA, Kaas L, Waterval JJ *et al.* Successful treatment of periungual warts using photodynamic therapy: a pilot study. *J Eur Acad Dermatol Venereol* 2007; **21**:1170–4.
141 Stefanaki IM, Georgiou S, Themelis GC *et al.* *In vivo* fluorescence kinetics and photodynamic therapy in condylomata acuminata. *Br J Dermatol* 2003; **149**:972–6.
142 Wang XL, Wang HW, Wang HS *et al.* Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol* 2004; **151**:880–5.
143 Herzinger T, Wienecke R, Weisenseel P *et al.* Photodynamic therapy of genital condyloma in men. *Clin Exp Dermatol* 2005; **31**:51–3.
144 Chen K, Chang BZ, Ju M *et al.* Comparative study of photodynamic therapy vs. CO_2 laser vaporization in treatment of condylomata acuminata: a randomized clinical trial. *Br J Dermatol* 2007; **156**:516–20.
145 Enk CD, Fritsch C, Jonas F *et al.* Treatment of cutaneous leishmaniasis with photodynamic therapy. *Arch Dermatol* 2003; **139**:432–4.
146 Ghaffarifar F, Jorjani O, Mirshams M *et al.* Photodynamic therapy as a new treatment of cutaneous leishmaniasis. *East Mediterr Health J* 2006; **12**:902–8.
147 Gardlo K, Horska Z, Enk CD *et al.* Treatment of cutaneous leishmaniasis by photodynamic therapy. *J Am Acad Dermatol* 2003; **48**:893–6.
148 Sohl S, Kauer F, Paasch U, Simon JC. Photodynamic treatment of cutaneous leishmaniasis. *J Dtsch Dermatol Ges* 2007; **5**:128–30.
149 Asilian A, Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. *Clin Exp Dermatol* 2006; **31**:634–7.
150 Kosaka S, Akilov OE, O'Riordan K, Hasan T. A mechanistic study of delta-aminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis. *J Invest Dermatol* 2007; **127**:1546–9.
151 Abok K, Cadelas E, Brunk U. An experimental model system for leishmaniasis. Effects of porphyrin-compounds and menadione on leishmania parasites engulfed by cultured macrophages. *APMIS* 1998; **96**:543–51.
152 Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. Lack of efficacy and tolerability of topical PDT for psoriasis in comparison with narrowband UVB phototherapy. *Clin Exp Dermatol* 2004; **29**:560–2.

153 Fransson J, Ros AM. Clinical and immunohistochemical evaluation of psoriatic plaques treated with topical 5-aminolaevulinic acid photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2005; **21**:326–32.

154 Radakovic-Fijan S, Blecha-Thalhammer U, Schleyer V *et al.* Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol* 2005; **152**:279–83.

155 Schleyer V, Radakovic-Fijan S, Kerrer S *et al.* Disappointing results and low tolerability of photodynamic therapy with topical 5-aminolaevulinic acid in psoriasis A randomized, double-blind phase I/II study. *J Eur Acad Dermatol Venereol* 2006; **20**:823–8.

156 Yim YC, Lee ES, Chung PS, Rhee CK. Recalcitrant palmoplantar pustular psoriasis successfully treated with topical 5-aminolaevulinic acid photodynamic therapy. *Clin Exp Dermatol* 2005; **30**:723–4.

157 Kim JY, Kang HY, Lee ES, Kim YC. Topical 5-aminolaevulinic acid photodynamic therapy for intractable palmoplantar psoriasis. *J Dermatol* 2007; **34**:37–40.

158 Fisher G, Kang S, Varani J *et al.* Mechanisms of photoaging and chronological skin aging. *Arch Dermatol* 2002; **138**:1462–70.

159 Ruiz-Rodriguez R, SanzSanchez T, Cordoba S. Photodynamic photorejuvenation. *Dermatol Surg* 2002; **28**:742–4.

160 Griffiths C, Wang TS, Hamilton TA *et al.* A photonumeric scale for the assessment of cutaneous photodamage. *Arch Dermatol* 1992; **128**:347–51.

161 Dover J, Bhatia AC, Stewart B, Arndt KA. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. *Arch Dermatol* 2005; **141**:1247–52.

162 Gold M, Bradshaw VL, Boring MM *et al.* Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. *Dermatol Surg* 2006; **32**:795–801.

163 Ruiz-Rodriguez R, Lopez-Rodriguez L. Nonablative skin resurfacing: the role of PDT. *J Drugs Dermatol* 2006; **5**:756–62.

164 Karrer S, Abels C, Landthaler M, Szeimies RM. Topical photodynamic therapy for localized scleroderma. *Acta Derm Venereol (Stockh)* 2000; **80**:26–7.

165 Karrer S, Bosserhoff AK, Weiderer P *et al.* Influence of 5-aminolevulinic acid and red light on collagen metabolism of human dermal fibroblasts. *J Invest Dermatol* 2003; **120**:325–31.

166 Karrer S, Bosserhoff AK, Weiderer P *et al.* Keratinocyte-derived cytokines after photodynamic therapy and their paracrine induction of metalloproteinases in fibroblasts. *Br J Dermatol* 2004; **151**:776–83.

167 Takahashi H, Komatsu S, Ibe M *et al.* ATX-S10(Na)-PDT shows more potent effect on collagen metabolism of human normal and scleroderma dermal fibroblasts than ALA-PDT. *Arch Dermatol Res* 2006; **298**:257–63.

168 Stender IM, Wulf HC. Photodynamic therapy with 5-aminolaevulinic acid in the treatment of actinic cheilitis. *Br J Dermatol* 1996; **135**:454–6.

169 Hauschild A, Lischner S, Lange-Asschenfeldt B, Egberts F. Treatment of actinic cheilitis using photodynamic therapy with methyl aminolevulinate: report of three cases. *Dermatol Surg* 2005; **31**:1344–7.

170 Berking C, Herzinger T, Flaig MJ *et al.* The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study in 15 patients. *Dermatol Surg* 2007; **33**:825–30.

171 Nayeemuddin FA, Wong M, Yell J, Rhodes LE. Topical photodynamic therapy in disseminated superficial actinic porokeratosis. *Clin Exp Dermatol* 2002; **27**:703–6.

172 Cavicchini S, Tourlaki A. Successful treatment of disseminated superficial actinic porokeratosis with methyl aminolevulinate-photodynamic therapy. *J Dermatolog Treat* 2006; **17**:190–1.

173 Berroeta L, Lewis-Jones MS, Evans AT, Ibbotson SH. Woringer–Kolopp (localized pagetoid reticulosis) treated with topical photodynamic therapy (PDT). *Clin Exp Dermatol* 2005; **30**:446–7.

174 Schmook T, Budde K, Ulrich C *et al.* Successful treatment of nephrogenic fibrosing dermopathy in a kidney transplant recipient with photodynamic therapy. *Nephrol Dial Transplant* 2005; **20**:220–2.

175 Ruiz-Rodriguez R, Alvarez JG, Jaén P *et al.* Photodynamic therapy with 5-aminolevulinic acid for recalcitrant familial benign pemphigus (Hailey–Hailey disease). *J Am Acad Dermatol* 2002; **45**:740–2.

176 Exadaktylou D, Kurwa HA, Calonje E, Barlow RJ. Treatment of Darier's disease with photodynamic therapy. *Br J Dermatol* 2003; **149**:606–10.

177 van't Westeinde SC, Sanders CJ, van Weelden H. Photodynamic therapy in a patient with Darier's disease. *J Eur Acad Dermatol Venereol* 2006; **20**:870–2.

178 Kirby B, Whitehurst C, Moore JV, Yates VM. Treatment of lichen planus of the penis with photodynamic therapy. *Br J Dermatol* 1999; **141**:765–6.

179 Hillemanns P, Untch M, Pröve F *et al.* Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid. *Obstet Gynecol* 1999; **93**:71–4.

180 Alexiades-Armenakas M. Laser-mediated photodynamic therapy of lichen sclerosus. *J Drugs Dermatol* 2004; **3**:S25–7.

181 Karrer S, Abels C, Wimmershoff MB *et al.* Successful treatment of cutaneous sarcoidosis using topical photodynamic therapy. *Arch Dermatol* 2002; **138**:581–4.

182 Heidenheim M, Jemec GBE. Successful treatment of necrobiosis lipoidica diabeticorum with photodynamic therapy. *Arch Dermatol* 2006; **142**:1548–50.

183 Mallipeddi R, Chaudhry SI, Darley CR, Kurwa HA. A case of focal dermal hypoplasia (Goltz) syndrome with exophytic granulation tissue treated by curettage and photodynamic therapy. *Clin Exp Dermatol* 2006; **31**:228–31.

184 Nybaek H, Jemec GB. Photodynamic therapy in the treatment of rosacea. *Dermatology* 2005; **211**:135–8.

185 Katz B, Patel V. Photodynamic therapy for the treatment of erythema, papules, pustules, and severe flushing consistent with rosacea. *J Drugs Dermatol* 2006; **5** (Suppl. 2):6–8.

186 Richey DF, Hopson B. Photodynamic therapy for perioral dermatitis. *J Drugs Dermatol* 2006; **5** (Suppl. 2):12–16.

187 Escudero A, Nagore E, Sevila A *et al.* Chronic X-ray dermatitis treated by topical 5-aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 2002; **147**:394–5.

188 Clayton TH, Harrison PV. Photodynamic therapy for infected leg ulcers. *Br J Dermatol* 2007; **156**:384–5.

189 Moiin A. Photodynamic therapy for molluscum contagiosum infection in HIV-co-infected patients: review of 6 patients. *J Drugs Dermatol* 2003; **2**:637–9.

190 Gold MH, Boring MM, Bridges TM *et al.* The successful use of ALA-PDT in the treatment of recalcitrant molluscum contagiosum. *J Drugs Dermatol* 2004; **3**:187–90.

191 Karrer S, Szeimies RM, Abels C *et al.* Epidermodysplasia verruciformis treated using topical 5-aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 1999; **140**:935–8.

192 Darras-Vercambre S, Carpentier O, Vincent P *et al.* Photodynamic action of red light for treatment of erythrasma: preliminary results. *Photodermatol Photoimmunol Photomed* 2006; **22**:153–6.

193 Calzavara-Pinton PG, Venturini M, Capezzera R *et al.* Photodynamic therapy of interdigital mycoses of the feet with topical application of 5-aminolevulinic acid. *Photodermatol Photoimmunol Photomed* 2004; **20**:144–7.
194 Wiegell SR, Kongshoj B, Wulf HC. *Mycobacterium marinum* infection cured by photodynamic therapy. *Arch Dermatol* 2006; **142**:1241–2.
195 Grapengiesser S, Ericson M, Gudmundsson F *et al.* Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol* 2002; **27**:493–7.
196 Sandberg C, Stenquist B, Rosdahl I *et al.* Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Derm Venereol (Stockh)* 2006; **86**:404–8.
197 Rud E, Gederaas O, Høgset A, Berg K. 5-Aminolevulinic acid, but not 5-aminolevulinic acid esters, is transported into adenocarcinoma cells by system BETA transporters. *Photochem Photobiol* 2000; **71**:640–7.
198 Wiegell S, Stender IM, Na R, Wulf HC. Pain associated with photodynamic therapy using 5-aminolevulinic acid or 5-aminolevulinic acid methylester on tape-stripped normal skin. *Arch Dermatol* 2003; **139**:1173–7.
199 Wiegell SR, Skiveren PA, Philipsen PA, Wulf HC. Pain during photodynamic therapy is associated with protoporphyrin IX fluorescence and fluence rate. *Br J Dermatol* 2008; **158**:727–33.
200 Kasche A, Luderschmidt S, Ring J, Hein R. Photodynamic therapy induces less pain in patients treated with methyl aminolevulinate compared to aminolevulinic acid. *J Drugs Dermatol* 2006; **5**:353–6.
201 Ericson M, Sandberg C, Stenquist B *et al.* Photodynamic therapy of actinic keratosis at varying fluence rates: assessment of photobleaching, pain and primary clinical outcome. *Br J Dermatol* 2004; **151**:1204–12.
202 Babilas P, Knobler R, Hummel S *et al.* Variable pulse light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratoses: a prospective randomized controlled trial. *Br J Dermatol* 2007; **157**:111–17.
203 Holmes M, Dawe RS, Ferguson J, Ibbotson SH. A randomized, double-blind, placebo-controlled study of the efficacy of tetracaine gel (Ametop) for pain relief during topical photodynamic therapy. *Br J Dermatol* 2004; **150**:337–40.
204 Langan SM, Collins P. Randomized, double-blind, placebo-controlled prospective study of the efficacy of topical anaesthesia with a eutectic mixture of lignocaine 2·5% and prilocaine 2·5% for topical 5-aminolaevulinic acid-photodynamic therapy for extensive scalp actinic keratoses. *Br J Dermatol* 2006; **154**:146–9.
205 Pagliaro J, Elliott T, Bulsara M *et al.* Cold air analgesia in photodynamic therapy of basal cell carcinomas and Bowen's disease: an effective addition to treatment: a pilot study. *Dermatol Surg* 2004; **30**:63–6.
206 Brooke RCC, Sinha A, Sidhu MK *et al.* Histamine is released following aminolevulinic acid-photodynamic therapy of human skin and mediates an aminolevulinic acid dose-related immediate inflammatory response. *J Invest Dermatol* 2006; **126**:2296–301.
207 Kerr AC, Ferguson J, Ibbotson SH. Acute phototoxicity with urticarial features during topical 5-aminolaevulinic acid photodynamic therapy. *Clin Exp Dermatol* 2007; **32**:201–2.
208 Verrico AK, Haylett AK, Moore JV. *In vivo* expression of the collagen-related heat shock protein HSP47, following hyperthermia or photodynamic therapy. *Lasers Med Sci* 2001; **16**:192–8.
209 Haylett AK, Higley K, Chiu M *et al.* Collagen secretion after photodynamic therapy versus scar-inducing anticancer modalities: an *in vitro* study. *Photochem Photobiol Sci* 2002; **1**:673–7.
210 Monfrecola G, Procaccini EM, d'Onofrio D *et al.* Hyperpigmentation induced by topical 5-aminolaevulinic acid plus visible light. *J Photochem Photobiol B* 2002; **68**:147–55.
211 Moseley H, Ibbotson I, Woods J *et al.* Clinical and research applications of photodynamic therapy in dermatology: experience of the Scottish PDT centre. *Lasers Surg Med* 2006; **38**:403–16.
212 Babilas P, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology. *Eur J Dermatol* 2006; **16**:340–8.
213 Morton CA, Whitehurst C, McColl JH *et al.* Photodynamic therapy for large or multiple patches of Bowen's disease and basal cell carcinoma. *Arch Dermatol* 2001; **137**:319–24.
214 Fritsch C, Goerz G, Ruzicka T. Photodynamic therapy in dermatology. *Arch Dermatol* 1998; **134**:207–14.
215 Chung WY, Lee JM, Lee WY *et al.* Protective effects of hemin and tetrakis (4-benzoic acid) porphyrin on bacterial mutagenesis and mouse skin carcinogenesis induced by 7,12-dimethylbenz[a] anthracene. *Mutat Res* 2000; **472**:139–45.
216 Fuchs J, Weber S, Kaufmann R. Genotoxic potential of porphyrin type photosensitizers with particular emphasis on 5-aminolevulinic acid: implications for clinical photodynamic therapy. *Free Radic Biol Med* 2000; **28**:537–48.
217 Finlan LE, Kernhan NM, Thomson G *et al.* Differential effects of 5-aminolaevulinic acid photodynamic therapy and psoralen + ultraviolet A therapy on p53 phosphorylation in normal skin *in vivo*. *Br J Dermatol* 2005; **153**:1001–10.
218 Takahashi H, Nakajima S, Sakata I *et al.* ATX-S10(Na)-photodynamic therapy is less carcinogenic for mouse skin compared with ultraviolet B irradiation. *Br J Dermatol* 2005; **153**:1182–6.
219 Wolf P, Fink-Puches R, Reimann-Weber A, Kerl H. Development of malignant melanoma after repeated topical photodynamic therapy with 5-aminolevulinic acid at the exposed site. *Dermatology* 1997; **194**:53–4.
220 Maydan E, Nootheti PK, Goldman MP. Development of a keratoacanthoma after topical photodynamic therapy with 5-aminolevulinic acid. *J Drugs Dermatol* 2006; **5**:804–6.
221 Wulf HC, Philipsen P. Allergic contact dermatitis to 5-aminolaevulinic acid methylester but not to 5-aminolaevulinic acid after photodynamic therapy. *Br J Dermatol* 2004; **150**:143–5.
222 Harries MJ, Street G, Gilmour E *et al.* Allergic contact dermatitis to methyl aminolevulinate (Metvix®) cream used in photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2007; **23**:35–6.
223 Hohwy T, Andersen KE, Sølvsten H, Sommerlund M. Allergic contact dermatitis to methyl aminolevulinate after photodynamic therapy in 9 patients. *Contact Dermatitis* 2007; **57**:321–3.
224 Golub AL, Gudgin DE, Kennedy JC *et al.* The monitoring of ALA-induced protoporphyrin IX accumulation and clearance in patients with skin lesions by *in vivo* surface-detected fluorescence spectroscopy. *Lasers Med Sci* 1999; **14**:112–22.
225 Angell-Peterson E, Christensen C, Mullet CR, Warloe T. Phototoxic reaction and porphyrin fluorescence in skin after topical application of methyl aminolaevulinate. *Br J Dermatol* 2006; **156**:301–7.
226 Ramrakha-Jones VS, Herd RM. Treating Bowen's disease: a cost-minimization study. *Br J Dermatol* 2003; **148**:1167–72.
227 Weston A, FitzGerald P. Discrete choice experiment to derive willingness to pay for methyl aminolevulinate photodynamic therapy versus simple excision in basal cell carcinoma. *Pharmacoeconomics* 2004; **22**:1195–208.
228 Caekelbergh K, Annemans L, Lambert J, Roelands R. Economic evaluation of methyl aminolaevulinate photodynamic therapy in the management of actinic keratoses and basal cell carcinoma. *Br J Dermatol* 2006; **155**:784–90.
229 Clayton TH, Tait J, Whitehurst C, Yates VM. Photodynamic therapy for superficial basal cell carcinoma and Bowen's disease. *Eur J Dermatol* 2006; **16**:39–41.

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
II-i	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group
II-iii	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 (e.g. sample size, or length of comprehensiveness of follow-up or conflicts in evidence)

