

REVIEW ARTICLE

European guidelines for topical photodynamic therapy part 2: emerging indications – field cancerization, photorejuvenation and inflammatory/infective dermatoses

C.A. Morton,^{1,*} R.-M. Szeimies,² A. Sidoroff,³ L.R. Braathen⁴

¹Department of Dermatology, Stirling Community Hospital, Stirling, UK

²Klinik für Dermatologie und Allergologie, Klinikum Vest GmbH, Behandlungszentrum, Knappschaftskrankenhaus Recklinghausen, Recklinghausen, Germany

³Department of Dermatology and Venereology, Medical University of Innsbruck, Austria

⁴Department of Dermatology, Bern, Switzerland

*Correspondence: C.A. Morton. E-mail: colin.morton@nhs.net

Abstract

In addition to established indications in non-melanoma skin cancer in immunocompetent patients, photodynamic therapy (PDT) has been studied for the treatment, and possible prevention, of superficial skin cancers in immunosuppressed patients. As a topical photosensitizer can be applied over large areas, PDT is also increasingly used for field cancerization in photodamaged skin, with evidence of potential to delay the development of actinic keratoses and basal cell carcinoma, although direct evidence of prevention of invasive squamous cell carcinoma remains limited. PDT has been studied in patch/plaque-stage cutaneous T-cell lymphoma, with efficacy more likely in unilesional disease. Accumulating evidence supports the use of PDT in acne and several other inflammatory/infective dermatoses including cutaneous leishmaniasis, although protocols are still to be refined. Despite proven efficacy, PDT is not widely used in viral/genital warts, where pain during treatment can be intense. PDT is a therapeutic option for photorejuvenation, with improvement in fine wrinkles, mottled hyperpigmentation, roughness and sallowness reported.

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Conflict of interest

CA Morton has received speaker honoraria from Galderma and served as a consultant to Almirall and Leo Pharma. RM Szeimies has served as a consultant for, and has received speakers' honoraria and financial support to perform clinical trials from Almirall, Biofrontera, Galderma, Leo, photodynamic and Spirig. The other authors declare no conflicts of interest.

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Disclaimer

The following guidelines are based on the best evidence available at the time of publication and caution should be exercised when interpreting data where there is a limited evidence base. It may be necessary to depart from the guidelines in the interests of specific patients and circumstances.

Introduction

This guideline seeks to promote safe and effective practice across Europe for the delivery of PDT in emerging dermatological indications and reflects evidence derived from a systematic literature review (using MEDLINE), and previous therapy guidelines, and

should be read in conjunction with Part I, which covers protocols, side-effects and PDT in established indications.^{1–3}

PDT typically involves the topical application of the photosensitizer prodrug, aminolaevulinic acid (ALA) or its methylated ester, MAL, converted by the haem biosynthetic pathway predominantly

to protoporphyrin IX (PpIX) and activated by light of an appropriate wavelength to produce reactive oxygen species, especially singlet oxygen, triggering both apoptosis and necrosis of target cells. PDT also acts as a biological response modifier by induction of innate and adaptive host immune responses, which may impact on the efficacy of PDT in immunocompromised patients.⁴ New formulations and novel photosensitizers have been studied, including a comparison of topical indocyanine green with indole-3-acetic acid in the treatment of acne, with the agents being equally effective.⁵ Light sources employed are predominantly the same light emitting diode (LED) sources used for current indications reviewed in Part I, although filtered intense pulsed lights (IPL) have been used in acne and photorejuvenation.¹ PDT can be painful when used for inflammatory/infective dermatoses and protocols must balance efficacy with tolerability.^{6,7}

PDT for the treatment of non-melanoma skin cancer in organ transplant recipients (Strength of recommendation B, Quality of evidence I)

Two PDT treatments 1 week apart were used to treat multiple actinic keratoses (AK) in 17 organ transplant recipients (OTR), with two 4 × 4-cm areas treated using either MAL or placebo cream. All AK were cleared in 13, with partial response in a further three patients, but placebo cream had no effect.⁸ In another study in OTR, two MAL-PDT treatments cleared 71% AK at 3 months, although response was lower for acral lesions (40%).⁹ ALA-PDT cleared 30/32 facial tumours [21 basal cell carcinoma (BCC), 8 AK, 1 keratoacanthoma] in five OTR patients after one to three treatments, although two invasive squamous cell carcinomas (SCC) did not respond.¹⁰

A comparison of ALA-PDT for AK and Bowen's disease (BD) between OTR and immunocompetent individuals showed similar 4-week clearance rates of 86% and 94%, respectively, but by 48 weeks, the OTR response rate had reduced to 48% compared with 72% in the immunocompetent patients, supporting the role of immune response factors in contributing to the mechanism of action of PDT.¹¹ PDT using MAL was more effective than topical 5-fluorouracil (5-FU) for epidermal dysplasias in OTR in a small randomized inpatient comparison study.¹² At 6-month follow-up, PDT had cleared 8/9 lesion areas, compared with only 1/9 areas treated by 5-FU (lesional area reduction: PDT 100%, 5-FU: 79%).

PDT for the prevention of non-melanoma skin cancer in organ transplant recipients (Strength of recommendation B, Quality of evidence I)

A single treatment of MAL-PDT significantly delayed (9.6 vs. 6.8 months for control site) development of new lesions in an inpatient randomized study of 27 renal OTR with AK and other skin lesions.¹³ By 12 months, 62% of treated areas were free from new lesions compared with 35% in control areas. A multicentre inpatient study of multiple treatments of MAL-PDT vs. no

treatment in 81 OTR showed an initial significant reduction in new lesions (65 vs. 103 in the control area), mainly AK, but this effect was lost by 27 months.¹⁴ Following two treatments, 1 week apart, PDT was repeated at 3, 9 and 15 months, suggesting that additional treatments are required to maintain a protective effect.

No significant difference in the occurrence of SCC was observed in a study of ALA-PDT vs. no treatment after 2 years follow-up in 40 OTR, although less penetrating blue light was used and there was no site preparation pre-PDT.¹⁵ However, another study used blue light and short 1-h incubation ALA-PDT, repeated at 4- to 8-week intervals for 2 years, observing a reduction in the incidence of SCC in 12 OTRs, compared with the number developing in the year prior to treatment, with a mean reduction at 12 and 24 months of 79% and 95%.¹⁶

PDT for field cancerization (Strength of recommendation B, Quality of evidence I)

Skin field cancerization, the presence of multiple non-melanoma skin cancer, AK and dysplastic keratinocytes in sun-exposed areas, reflects the presence of multilocal clinical and subclinical cancerous lesions. Field therapies, including PDT are most appropriate for treating field cancerization.¹⁷ A recent consensus noted that PDT in field cancerization treatment in OTR might also prevent new AKs and the transformation of AK to invasive SCC in a secondary prevention strategy, proposing cyclic PDT with at least two initial treatments repeated several times over a year, possibly at 3 monthly intervals.¹⁸

The preventive potential of field PDT in immunocompetent individuals was studied in photodamaged patients with facial AK, where ALA-PDT demonstrated a significant delay over control sites of about 6 months until new AK developed.¹⁹ PDT can decrease expression of p53, a marker of early skin cancer, supporting its preventive indication in carcinogenesis.^{20,21}

Cutaneous T-cell lymphoma (Strength of recommendation C, Quality of evidence IIIii)

Topical ALA- and MAL-PDT have both been used in localized cutaneous T-cell lymphoma, with selective uptake of photosensitizers into lymphocytes observed.³ Evidence is derived from case reports and series, with no standardization of protocol. Remission was observed in four of five patients with unilesional disease, with partial response in the remaining patient, following MAL-PDT in the same dosimetry as for BCC, but repeated once weekly, with a median of six treatments required (range 1–9).²² Multiple (median 2, range 2–11) ALA-PDT treatments has also been observed to clear plaque (7/9), but not tumour (0/2) disease in a series of 10 patients.²³ An adjuvant role for PDT was demonstrated in patients with extensive erosive facial mycosis fungoides, where multiple treatments with MAL-PDT achieved marked local improvement.²⁴

Topical PDT using ALA ($n = 2$) and MAL ($n = 1$) has also achieved clinical and histological remission after one or two treat-

ments in three patients with localized thin plaque cutaneous B-cell lymphoma, with clearance maintained over 8–24 months.²⁵

Extra-mammary Paget's disease (Strength of recommendation D, Quality of evidence III)

Topical PDT appears to have a limited role as monotherapy in extramammary Paget's disease (EMPD), although case reports and small series demonstrate at least short-term improvement. ALA-PDT initially cleared 8/16 EMPD lesions in five patients at 6 months, but with three recurring after a further 3–4 months.²⁶ A further two cases of EMPD responded to ALA-PDT, and seven patients with recurrent EMPD of the vulva were treated using MAL-PDT and red light, with clearance in four.^{27,28} PDT with the ALA applied via a bioadhesive patch cleared vulval EMPD after four treatments, with histological confirmation.²⁹

Topical PDT for infectious and inflammatory dermatoses

Acne (Strength of recommendation A, quality of evidence I)

PDT has been extensively studied in acne, yet without consensus on optimal protocol. Protocols employing lower drug concentrations, low light doses (e.g. 13 J/cm² 600–700 nm), short incubation and/or less penetrating blue light, 'low dose' PDT, are probably more likely to achieve a shorter term effect via direct antimicrobial or immunomodulatory effects. In contrast, 'high dose' PDT (e.g. 150 J/cm² 550–700 nm) probably promotes direct destruction of sebaceous glands.³⁰ Follicular obstruction may be reduced by enhanced epidermal turnover promoted by PDT. *Propionibacterium acnes* naturally produces small amounts of certain porphyrins, especially coproporphyrin III, with topical ALA application promoting accumulation.³¹ However, certain studies have failed to show a reduction, or only a temporary reduction in *p.acnes* after PDT, while a decrease in sebum excretion has been observed more consistently.³⁰

A recent critical analysis of PDT studies in acne concluded that high-dose ALA- and MAL-PDT produce similar effects, that photosensitizer incubation of three or more hours was associated with long-term remission, that red light is more likely to promote sebaceous gland destruction compared with blue or pulsed light and that treatment was often painful and induced marked inflammation.³²

Several open studies report ALA-PDT in facial acne using a range of application times from 0.25–4 h and several light sources including blue light and IPL.³³ Protocol variations, some including preparatory peels, small patient numbers and short follow-up, limit interpretation of these studies, with the extent of accumulation of photoactive porphyrins after short applications yet to be determined.

In a randomized study of 36 patients with moderate-to-severe acne, MAL-PDT with prior gentle lesion curettage, repeated

2 weeks later, achieved a 68% reduction in inflammatory lesions at 3 months, with no change in the control group, but no reduction in non-inflammatory counts.³⁴ All patients experienced moderate-to-severe pain and developed erythema, pustular eruptions and epithelial exfoliation. A randomized split-face comparison study of 15 patients, by the same group, of a single treatment of ALA- and MAL-PDT achieved a 59% reduction in inflammatory lesions after 3 months in both groups, but with moderate-to-severe pain and pustular reactions, more severe following ALA-PDT.⁸ A further randomized split-face study of MAL-PDT (repeated after 2 weeks) in 30 patients with moderate-to-severe facial acne showed a 54% reduction in inflammatory lesions (placebo – 20%).³⁵

Research continues to identify the optimal protocol that achieves efficacy yet minimizes adverse effects, with the likely need to combine with a therapy more effective in reducing non-inflamed lesions. A small 16-patient study observed a 66% reduction in inflamed lesions (no difference in non-inflamed) 12 weeks after 2–3 MAL-PDT treatments at fortnightly intervals using a more dilute 4% formulation of MAL and reduced red light dose of 10–20 J/cm² delivered after 1.5-h incubation.³⁶ A mean decrease of 71% of inflamed and 66% of non-inflamed lesions was achieved in a randomized study using a 0.5% 5-ALA liposomal spray and IPL as well as topical keratolytic agents after a mean of 5.7 treatments.³⁷

MAL-PDT has also been reported as effective in chronic folliculitis in a case series of seven patients.³⁸ Several case reports/series observe PDT to be effective in sebaceous hyperplasia.^{39–42} Variable efficacy has been reported for PDT in hidradenitis suppurativa. Although in one series of four patients no one achieved significant improvement after ALA-PDT, another study reported improvement of 75–100% in four patients using blue light ALA-PDT.^{43,44}

Experience of PDT in rosacea is limited, but MAL-PDT achieved good results in 10/17 patients.⁴⁵ A prospective case series compared pulse dye laser-assisted MAL-PDT with laser alone for rosacea, with no difference in response.⁴⁶

PDT for refractory hand and foot warts (Strength of recommendation B, Quality of evidence I)

Several studies have demonstrated high efficacy of PDT for viral warts, yet few practitioners use it routinely, probably on account of the current absence of an optimized protocol combining high cure rates with good tolerability. Clearance rates of recalcitrant hand and foot warts of 56–100% have been achieved, with superiority of six repetitive ALA-PDT treatments to placebo (where standard paring and topical keratolytic were applied in both groups) in a randomized trial resulting in a median reduction in wart area of 98% with PDT and 52% by 'placebo', although PDT induced intense pain in some patients.⁴⁷ PDT has been shown to achieve superior clearance to cryotherapy in a randomized pilot study of ALA-PDT in 30 patients with recalcitrant warts.⁴⁸ A study compared the treatment of verrucae by ALA-PDT using

either a pulse dye laser (PDL) or LED source, with the use of PDL alone, with clearance rates of 100%, 96% and 81% respectively.⁴⁹

Success of ALA-PDT in a patient with multiple facial plane warts has been reported, following two treatments, confirmed by a recent case series using a 10% ALA formulation with clearance of facial warts in 17/18 patients after two sessions and only one recurrence after 6 months.^{50,51} Complete clearance of periungual hand warts in 18/20 patients (36/40 warts) was achieved using ALA-PDT after a mean of 4.5 fortnightly treatments.⁵² MAL-PDT dramatically cleared a recalcitrant hand wart in a case report, but literature remains limited on its use in warts.⁵³

PDT for genital warts (Strength of recommendation B, Quality of evidence I)

Topical PDT is a treatment option for patients with genital warts. Clearance rates of 73% and 66% were reported following ALA-PDT in a series of men with condyloma acuminata and in 16 women with vulvar and vaginal condylomata.^{54,55} In a large study of 164 patients with urethral condylomata, one to four ALA-PDT treatments cleared 95% of lesions, with only 5% recurring after 6–24 months.⁵⁶

A randomized study compared ALA-PDT with conventional CO₂ laser in 65 patients with condyloma acuminata with a single treatment clearing 95% and 100% of lesions, respectively, and persisting lesions clearing following repeat PDT.⁵⁷ A lower recurrence rate followed PDT (6% vs. 19%). In a larger randomized trial of ALA-PDT of 90 patients with condylomata acuminata, all lesions cleared in each arm of the study (PDT vs. CO₂ laser) with fewer recurrences after PDT (9% vs. 17% at 3 months), the authors concluding that PDT was a simpler, better tolerated, treatment.⁵⁸ However, in the largest prospective, randomized trial with 175 patients, where ALA-PDT was used as an adjunctive treatment to ablation with the CO₂-laser, cumulative recurrence rate 12 weeks after treatment was 50% in the laser+PDT group vs. 53% in the PDT-only group, thus indicating that despite good tolerance, ALA-PDT may not add benefit to CO₂-laser vaporization of condyloma.⁵⁹

Cutaneous Leishmaniasis (Strength of recommendation B, Quality of evidence I)

In a review of six studies in which a total of 39 patients with 77 lesions of cutaneous leishmaniasis received ALA-PDT or MAL-PDT, healing of lesions was achieved in 94–100%.⁶⁰ In the largest study of 11 patients (32 lesions), one or two weekly treatments with red light ALA-PDT rendered smears amastigote negative, with no relapses over 6 months.⁶¹

In a randomized trial of 57 patients, receiving weekly red light ALA-PDT, twice-daily topical paromomycin or placebo, each over 4 weeks, lesion clearance (and parasitological cure rate by smear) at 8 weeks was seen in 94% (100%), 41% (65%) and 13% (20%) respectively.⁶²

A mechanistic study concluded that response to PDT is likely to be due to non-specific tissue destruction and 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.^{63,64}

Photodynamic photorejuvenation (Strength of recommendation B, Quality of evidence I)

Multiple studies, recently reviewed, have observed improvement in fine wrinkles, mottled hyperpigmentation, roughness and sallowness, following PDT, with observed upregulation of collagen production and increased epidermal proliferation.^{21,65} In a randomized split-face study, all subjects with a moderate or higher degree of photoageing received five full-face treatments with IPL, but with ALA applied as adjunctive treatment for 0.5–1 h to a randomly assigned hemiface before the first three treatments.⁶⁶ A significantly greater improvement in global score for photoageing, mottled pigmentation and fine lines was observed for the side receiving the combined therapies. A further split-face study compared ALA-IPL with IPL alone, given three times at monthly intervals in 13 subjects.⁶⁷ The ALA pretreated side showed enhanced improvement of fine lines, skin roughness, mottled hyperpigmentation and telangiectasias.

In a split-face study of PDL to both sides of the face, 1 h after ALA was applied to one side, improvement in softness and texture and disappearance of solar lentiginos was noted on the PDT-PDL side.⁶⁸

In a small randomized split-face study of MAL-PDT (1- vs. 3-h incubation) in 10 patients with moderate photodamage, the authors noted improvement in tactile roughness, fine lines and skin tightness in most patients on the side treated after 3-h incubation.⁶⁹ The same group has evaluated MAL-PDT (to one half of the perioral area) following fractional photothermolysis to both sides of the face, repeated at 3 weeks. Improvement in superficial rhytides and overall patient satisfaction was greater in the combined treatment side.⁷⁰ In a recent blinded, randomized controlled split-face study, MAL-PDT achieved superior efficacy in global facial photodamage.⁷¹

Other indications

There remains limited published data on PDT in many additional dermatoses. Case reports have been reviewed elsewhere, but we review conditions where larger case series (≥5 patients) have been published.³

ALA-PDT was effective in localized scleroderma in five patients, with induction of the collagen-degrading matrix metalloproteinase (MMP)-1 and MMP-3 by fibroblasts post-PDT.^{72,73} PDT using a bioadhesive patch containing ALA was used to treat patients with vulvar lichen sclerosis. Six of nine women reviewed at 6 weeks had significant improvement in pruritus, but no significant difference in histopathology was noted.⁷⁴ A case series of 12 patients with vulvar lichen sclerosis achieved improvement in pruritus following

ALA-PDT in 10 for a mean of 6 months.⁷⁵ In a series of six patients with Darier's disease treated by ALA-PDT, four patients showed improvement/clearance.⁷⁶

In a split-face comparison of blue-light ALA-PDT (four times weekly, 0.5-h incubation) vs. clindamycin for perioral dermatitis, PDT achieved superior clearance of 92% of lesions compared with 81% with clindamycin.⁷⁷ In a report of five patients with radiodermatitis, red light ALA-PDT induced remission in two and achieved a partial response in three.⁷⁸ Four of five patients with chondrodermatitis cleared following one MAL-PDT treatment using the standard protocol for AK.⁷⁹

Blue-light ALA-PDT was effective in reducing lesion counts in six HIV patients with molluscum contagiosum.⁸⁰ PDT has also been assessed in superficial mycoses. In a case series of nine patients with interdigital mycoses, there was initial clinical and mycological clearance in six, following one to four ALA-PDT treatments, however, recurrence was observed in four by 1 month.⁸¹ Another group recruited 10 patients with interdigital tinea pedis to receive up to three sessions of red-light ALA-PDT, with initial response in six, but only three had persistent healing at follow-up 2 months later.⁸² An initial response to ALA-PDT, followed by relapse within 8 weeks, occurred when treating 10 patients with tinea cruris.⁸³

PDT appears to have a limited role in treating psoriasis. A study of ALA-PDT in 12 patients with psoriasis showed improvement of 37.5, 45.6 and 51.2% in the 0.1, 1 and 5% ALA-treated groups respectively.⁸⁴ A study of four patients with psoriasis showed narrowband UVB to be superior to ALA-PDT.⁸⁵ Treatment with PDT was poorly tolerated with early termination of the trial. A randomized, observer blinded study of ALA-PDT for 21 patients with psoriasis also showed disappointing results with clearance/substantial improvement only in 12/63 plaques.⁸⁶

Multiple MAL-PDT can soften and improve the appearance and histological changes of hypertrophic scars.⁸⁷ A retrospective study of six field cancerization patients also observed significant improvement in appearance of pre-existing scars after two to three PDT treatments (ALA and MAL) suggesting that PDT may promote scar remodelling.⁸⁸

PDT – cost effectiveness

The cost of PDT will be influenced by clinic set-up, nurse/technician- vs. doctor-led therapy, drug and light choice, etc. A detailed analysis of cost per full responder calculated that MAL-PDT was cost effective in AK when compared with cryotherapy over 1 year, and better value in BCC compared with excision over 5 years to allow time for recurrences.⁸⁹ In a real-life practice study by the same group, total cost of care/patient was euro 381 for AK, 318 euro for nodular BCC and 298 euro for superficial BCC (cost/lesion: 58, 316,178 euros respectively) consistent with their model.⁹⁰ An analysis of the treatment of 67 patients with either BD or superficial BCC showed a mean saving over surgery of 322

euros/lesion treated by MAL-PDT (and 307 euros saved/lesion treated by imiquimod), although surgery was superior in efficacy at 2 years with clearance rates of 97.5% compared with 89.5% after PDT and 87.5% after imiquimod.⁹¹ A cost comparison from the perspective of the UK NHS for treating multiple AKs concluded that imiquimod cost £174 less over 1 year, but resulted in 0.005 fewer QALYs gained, the authors advising that a direct comparison study was needed.⁹² However, in a cost-consequences analysis comparing 5-FU, imiquimod and PDT for AK also under the perspective of the UK NHS, one cycle of MAL-PDT followed by various second-line options led to the greatest clinical response (92%), while two cycles of MAL-PDT led to the best overall cosmetic outcome.⁹³ Given the multiple patient scenarios within which PDT is used, even within currently licensed indications, summarizing cost-effectiveness remains a challenge, with new photosensitizer formulations and light sources likely to add pressure to trim drug/equipment costs.

Appendix 1

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

Appendix 2

Quality of evidence

- I. Evidence obtained from at least one properly designed, randomized control trial
- II-i Evidence obtained from well-designed control trials without randomization
- II-ii Evidence obtained from well-designed cohort or case-control analytic 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).

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