REVIEW ARTICLE

European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma

C.A. Morton,[1,*] R.-M. Szeimies,[2] A. Sidoroff,[3] L.R. Braathen[4]

[1]Department of Dermatology, Stirling Community Hospital, Stirling, UK
[2]Behandlungszentrum, Knappschaftskrankenhaus Recklinghausen, Klinik für Dermatologie und Allergologie, Klinikum Vest GmbH, Recklinghausen, Germany
[3]Department of Dermatology and Venereology, Medical University of Innsbruck, Austria
[4]Department of Dermatology, Bern, Switzerland
*Correspondence: C.A. Morton. E-mail: colin.morton@nhs.net

Abstract

Topical photodynamic therapy (PDT) is a widely used non-invasive treatment for certain non-melanoma skin cancers, permitting treatment of large and multiple lesions with excellent cosmesis. High efficacy is demonstrated for PDT using standardized protocols in non-hyperkeratotic actinic keratoses, Bowen's disease, superficial basal cell carcinomas (BCC) and in certain thin nodular BCC, with superiority of cosmetic outcome over conventional therapies. Recurrence rates following PDT are typically equivalent to existing therapies, although higher than surgery for nodular BCC. PDT is not recommended for invasive squamous cell carcinoma. Treatment is generally well tolerated, but tingling discomfort or pain is common during PDT. New studies identify patients most likely to experience discomfort and permit earlier adoption of pain-minimization strategies. Reduced discomfort has been observed with novel protocols including shorter photosensitizer application times and in daylight PDT for actinic keratoses.
Received: 27 June 2012; Accepted: 03 October 2012

Funding sources

None Declared

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 clinincal trials from Almirall, Biofrontera, Galderma, Leo, photonamic and Spirig. The other authors declare no conflicts of interest.

[Correction added on 30 November 2012, after first online publication: conflict of interest statement was amended.]

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 topical photodynamic therapy (PDT) in dermatological indications and reflects evidence derived from a systematic literature review (using MEDLINE), and previous therapy guidelines.[1,2] There is a substantial literature on novel indications for topical PDT and these are reviewed in Part II.[3]

Topical PDT has, to date, been approved for the treatment of certain non-melanoma skin cancers (NMSC). Currently, only three photosensitizing agents are licensed for use in Europe (Table 1). One is methyl aminolaevulinate (MAL) Metvix®/Metvixia® (Galderma, Lausanne, Switzerland). MAL is used along with red light to treat non-hyperkeratotic actinic keratoses (AK), Bowen's disease (BD), superficial and nodular basal cell

© 2012 The Authors

carcinomas (BCC), although approvals vary between countries. A patch containing 5-ALA (Alacare®; Spirig AG, Egerkingen, Switzerland) is approved for the treatment of mild AK in a single treatment session in combination with red light without pretreatment of the lesion, and BF-200 ALA (Ameluz®; Biofrontera AG, Leverkusen, Germany) is licensed for PDT in combination with red light. Another formulation of 5-ALA, Levulan (DUSA Pharmaceuticals, Wilmington, MA, USA), is approved in North America and certain other countries for AK, in a protocol that uses blue light. Many original studies of topical PDT used non-standardized preparations of aminolaevulinic acid (ALA) made in hospital pharmacies, so caution is advised in comparison of results.

Photosensitizers

PDT for dermatological indications, first described over 20 years ago, typically involves the topical application of the photosensitizer prodrug, ALA or its methylated ester MAL, which are converted by the haem biosynthetic pathway predominantly to protoporphyrin IX (PpIX) and activated by light of an appropriate wavelength, producing reactive oxygen species, especially singlet oxygen, resulting in apoptosis and necrosis of target tissue.[4] Selective uptake of the prodrugs is probably due to altered surface permeability over lesions and different rates of porphyrin metabolism, with activated lymphocytes also accumulating photosensitizer.[5,6]

ALA is hydrophilic whereas MAL is more lipophilic, and hence MAL may penetrate more deeply into lesions, although studies that have compared these agents when used to treat AK and nodular BCC failed to show a difference in response.[7,8] Recently, the nanoemulsion BF-200 ALA, which improves ALA stability and skin penetration, was compared with MAL for thin/moderate thickness face/scalp AK, with a higher patient complete clearance of 78% vs. 64% respectively.[9]

A self-adhesive, skin-coloured thin 5-ALA patch, directly applied to AK lesions without crust removal was superior to cryotherapy in clearing mild/moderate AK.[10]

Enhancing penetration of a photosensitizer using iontophoresis or chemical enhancers may increase the efficacy of PDT, but remains experimental. Elevating skin temperature during ALA application may also improve efficacy as PpIX production is a temperature-dependent process.[11]

MAL-PDT is delivered using a standardized protocol of two treatments 1 week apart for BCC and BD, but with only one initial treatment for AK, repeated at 3 months only if required.[12] MAL is typically applied for 3 h, but Levulan ALA although licensed for an 18–24 h application, is widely used with shorter application intervals around 1 h.[13] A shorter 1-h incubation for MAL-PDT in AK is also an option with no significant difference in clearance rates when compared (1 h:76%, 3 h:85%).[14]

Several novel topical photosensitizers including hypericin and silicon phthalocyanine have been assessed in a variety of cutaneous neoplasms, but await commercialization.[15–17]

Light sources and dosimetry

A range of light sources can be used for topical PDT including lasers, filtered xenon arc, metal halide or fluorescent lamps and light emitting diodes (LED). Large fields can be treated using narrowband LED devices, e.g. the Aktilite 128 (Galderma, Lausanne, Switzerland) and the Omnilux (Phototherapeutics Ltd, London, UK). These red LED sources match the 630/635-nm activation peak of PpIX while excluding the extraneous wavelengths present in broadband lights, thus permitting shorter illumination times. Filtered intense pulsed lights (IPLs) have been successfully used in PDT for AK, although phototoxic effects may not match cut-off filter notations provided by their manufacturers.[18] Narrow-spectrum light sources are associated with relatively higher response rates when compared with broad-spectrum devices, with complete patient clearance rates of 85% and 68% for BF-200 ALA-PDT or MAL-PDT, respectively, compared with 72% and 61% when broad-spectrum devices were used.[9,19]

Protoporphyrin IX has its largest absorption peak in the blue region at 410 nm with smaller absorption peaks at 505, 540, 580 and 630 nm. Most light sources for PDT seek to utilize the 630-nm red absorption peak, to improve tissue penetration. However, a blue fluorescent lamp (peak emission 417 nm) is used in Levulan-PDT.

Fractionation (discontinuous illumination) can improve tumour responsiveness by permitting tissue reoxygenation during 'dark' periods. Studies support the superiority of fractionation to conventional illumination in ALA-PDT for superficial BCC (97% vs. 89%), but not in Bowen's disease.[20,21] Overall clearance of 95% after 2 years was achieved for 552 NMSC lesions following ALA-PDT using two light fractions of 20 and 80 J/cm^2; at 4 and 6 h.[22] Another group has shown superior clearance of fractionated lesions by ALA-PDT (using the same protocol) at 3 months of 96% AK compared with 89% for lesions treated twice 7 days apart, with 12-month clearance rates of 94% and 85%.[23] An alternative ALA-PDT fractionation protocol of two doses of 75J/cm^2; at 4 and 5 h was associated with initial clearance of 94% nBCC, but with a cumulative failure rate of 30% by 3 years.[24]

PDT using daylight (MAL for 0.5 h, then daylight for 2.5 h) has been shown to be as effective as conventional red light MAL-PDT in AK, but with minimal or no therapy-related pain.[25] The same group has demonstrated no inferiority by reducing daylight exposure to 1.5 h in a study of thin AK, an observation replicated in another study of all severity grades of AK, although with poorer response rates for moderate and thick AK and variation in response between centres.[26,27] A recent international consensus highlighted the convenience of daylight PDT for patients with multiple AK requiring field therapy, but careful scheduling is required, giving consideration to time of the year when suitable daylight and tolerable weather conditions prevail, with use of an appropriate sunscreen to the entire sun-exposed area.[28]

There is also an option for ambulatory PDT where patients wear a portable LED light source with low irradiance over 100 min. In two small pilot studies, the device has been effective

© 2012 The Authors

in treating BD and sBCC, clearing 11 of 17 lesions with minimal pain in most.[29,30]

Lesion preparation

Gentle removal of overlying crust and scale is commonly performed for moderate thickness/hyperkeratotic AK, BD and sBCC when using MAL-PDT. Occlusion of lesions with a keratolytic the night before treatment can facilitate easier crust removal. Tape-stripping, microdermabrasion or laser ablation or gentle curettage can also be used to reduce hyperkeratosis. Some practitioners have observed reduced efficacy if lesions are not debrided prior to PDT,[11,14] whereas others have not noted increased drug uptake following lesion preparation of BD and BCC (in a study of 4- and 6-h ALA application possibly indicating reduced need with longer application times) and lesion preparation is not necessary when using a novel ALA patch.[10,31,32]

Preparation is probably more important when treating nodular BCC by PDT with recommended practice to gently remove overlying crust with a curette/scalpel in a manner insufficient to cause pain, and thus not requiring local anaesthesia. Some PDT operators perform a more significant preparation with debulking curettage, 3 weeks prior to ALA-PDT, clearing 92% of nBCC in a single treatment, although no comparison without prior curettage was made.[33] In a small comparison study of PDT (ALA and MAL) with or without debulking immediately before application of pre-photosensitizer, residual nBCC was more often observed in lesions that were not debulked.[7] Additional preparation techniques reported include microneedling, skin vapourization with CO_2 laser or ablative fractional resurfacing.[34–36]

Practitioners typically cover treatment sites with light occlusive dressings, on the presumption that full exposure to ambient light during the incubation period will lead to increased activation of PpIX superficially reducing deeper photosensitizer penetration before photoactivation. Occlusion is standard practice in MAL-PDT of AK, Bowens and BCC, but is not performed when using Levulan-ALA. When daylight was compared with conventional PDT, no difference in efficacy was noted between 0.5-h and 3-h occlusion intervals and recent studies recommend no occlusion, yet report equivalent efficacy in AK.[26]

Fluorescent diagnosis

The detection of skin surface fluorescence, either subjectively using simple handheld Wood's lamp (long wave UVA) or semiquantitatively using CCD camera systems coupled to digital imaging, is used to help delineate lesions and can be useful in identifying persistent/recurrent disease.[37,38] PpIX fluorescence imaging to determine tumour boundaries during Mohs micrographic surgery has shown inconsistent results regarding improvement in surgical efficacy.[39] Fluorescence diagnosis was not substantially superior to clinical assessment in a study of 28 BCC where tumours were excised on the basis of fluorescence outline with failure of correlation of the margin with histopathological tumour border in six lesions.[40]

Extent of photobleaching during PDT, but not total initial protoporphyrin IX fluorescence, is predictive of lesion clearance.[41] In another study, fluorescence diagnosis in keratinocyte intraepidermal neoplasias was unable to discriminate between lesions or proliferative activity.[42] Intensity of pain has been associated with fluorescence and may anticipate patients more likely to require anaesthesia.[43]

Actinic Keratoses (Strength of Recommendation A, Quality of Evidence I)

Thin and moderate thickness AK on the face and scalp respond well to topical PDT, with typical clearance rates of 89–92% 3 months after therapy, equivalent or superior to cryotherapy, depending on protocol.[44–46] One-year sustained lesion clearance rates of 78% and 63–69% have been reported following ALA-PDT (up to two treatments) and patch ALA-PDT (single treatment) respectively.[32,47]

Current licensed use recommends that for AK, MAL-PDT be given as a single treatment and repeated if required after 3 months, reflecting equivalent efficacy in a comparison study with double therapy 7 days apart.[45] A large randomized intraindividual study of face/scalp AK in 119 patients used this protocol to compare MAL-PDT with cryotherapy.[46] After the initial cycle of treatments, PDT cleared more lesions (87% vs. 76%), but with equivalent outcome after non-responders were retreated (89% vs. 86%).

Efficacy of PDT for AK on acral sites is reduced by approximately 10% to that for face/scalp lesions, probably in part due to a higher proportion of less-responsive thicker lesions on these sites. When compared, MAL-PDT was less effective than cryotherapy for acral AK (lesion clearance 78% vs. 88% at 6 months).[48] In a right/left comparison study with imiquimod, ALA-PDT cleared significantly more moderate AK lesions (58% vs. 37%), and equivalent numbers of thin AK on the hands/forearms (72% lesions).[49]

As reviewed above, several novel methods of delivering PDT have been used to treat AK, including the adhesive patch, daylight, ambulatory light sources and fractionated light protocols. Licensed recently, PDT using the BF-200 ALA was superior to MAL with clearance of 90% vs. 83% of thin/moderate thickness face/scalp AK (complete clearance rates of 78% vs. 64%) 12 weeks after one or two PDT treatments.[9]

PDT may be a useful therapy for patients with actinic cheilitis. Clearance was achieved in 26/40 patients after ALA-PDT (two treatments 2 weeks apart), although with histological recurrence in nine during 18 months of follow-up.[50] Two sessions of MAL-PDT 1 week apart achieved clinical clearance in 7/15 patients, although histological clearance was evident in only 4/7.[51] A recent study achieved superior results using sequential MAL-PDT then imiquimod 5% cream with complete clinical cure of 80% and histological cure of 73%.[52]

© 2012 The Authors

Guidelines identify PDT as effective both as a lesion and field-directed treatment for AK and suggest PDT has a role where AK are multiple and/or confluent, at sites of poor healing, or where there has been a poor response to other topical therapies.[53,54] In a randomized comparison of patient tolerance to MAL-PDT or topical imiquimod for multiple face/scalp AK, a significantly higher level of satisfaction was observed following PDT.[55]

Bowen's Disease (Strength of Recommendation A, Quality of Evidence I)

Invasive SCC (Strength of Recommendation D, Quality of Evidence II-iii)

A patient can expect clearance of 86–93% of BD lesions (squamous cell carcinoma in situ) 3 months beyond one or two cycles of MAL-PDT using red light, respectively, (two treatments 7 days apart as one cycle) with sustained clearance at 24 months of 68–71%, equivalent to conventional therapy, but with superior cosmesis.[56,57] Another study observed 76% clearance rate after two sessions of MAL-PDT and median follow-up of 16 months.[58]

MAL-PDT is effective in treating lesions over 3 cm, with 96% lesions cleared 3 months after one cycle of two treatments 7 days apart, with only three recurrences by 1 year.[59] PDT has been reported to clear digital, subungual and nipple BD and where it arises in a setting of poor healing (lower leg, epidermolysis bullosa and radiation dermatitis).[2] PDT may offer an alternative for treating penile intraepithelial neoplasia, with one large series using both ALA- and MAL-PDT in 10 patients showing clearance in 7, but later recurrence in 4.[60]

Therapy guidelines recommend PDT as the treatment of choice for both large and small plaques of BD on poor-healing sites, representing the majority of lesions, and a good choice for large lesions in good-healing sites.[61] There is reduced efficacy of PDT for microinvasive and for nodular invasive SCC, where 24-month clearance rates of 57% and 26% have been reported. The degree of cellular atypia is a negative prognostic factor, suggesting that poorly differentiated keratinocytes are less sensitive to PDT. In view of its metastatic potential and reduced efficacy rates, PDT currently cannot be recommended for invasive SCC.[57]

Superficial Basal cell carcinoma (Strength of Recommendation A, Quality of Evidence I)

Nodular Basal cell carcinoma (Strength of Recommendation A, Quality of Evidence I)

Clearance rates at 3 months of 92–97% following MAL-PDT for primary superficial BCC are observed with protocols of either one single initial treatment or two treatments 7 days apart, followed by a repeat two-treatment cycle at 3 months, if required.[62,63] Recurrence rates of 9% at 1 year were noted in both studies, with 22% of initially responding lesions recurring over 5 years of follow-up. A weighted initial clearance rate of 87% was noted for sBCC treated by ALA-PDT in a review of 12 studies, compared with 53% for nodular lesions.[64]

Thicker lesions appear less responsive to PDT and lesions in the H-zone also have reduced sustained clearance rates.[65,66] Clearance at 3 months of 91% of primary nBCC following MAL-PDT is reported, with 76% still clear at 5 years.[12,67]

Comparison of ALA-PDT with cryotherapy for BCC showed equivalent efficacy with superior cosmesis.[68] Clearance rates were also equivalent for MAL-PDT vs. cryotherapy for sBCC, 97% and 95% at 3 months, respectively, with overall clearance after 5 years identical at 76% of lesions initially treated, but with superior cosmesis post-PDT.[62]

MAL-PDT was equivalent to surgery (92% vs. 99% initial clearance, 9% and 0% recurrences at 1 year) for sBCC, but inferior to surgery for nBCC when recurrence rates were compared (91% vs. 98% initial clearance, 14% and 4% recurrences at 5 years).[63] Cosmetic outcome was superior following PDT compared with surgery. In a randomized pilot study of PDT with minimal curettage pre-ALA application vs. conventional surgery, there was no evidence of superiority of PDT over surgery.[69] Overall histologically confirmed response rates of 73% were reported following MAL-PDT for nBCC, using the standard licensed protocol, although 89% of facial BCC cleared.[70] A poorer response was reported in a large series of 194 BCC, with an 82% clearance rate for sBCC, but only 33% of nodular lesions clearing following MAL-PDT by standard protocol, although no debulking of the tumour mass was performed.[71]

Fractionated ALA-PDT was equivalent to surgery in initially clearing nBCC, but with a 30% failure rate over 3 years after PDT when a 75J/75J protocol was used, although in another study, 80% of nBCC remained clear at 2 years using a 20J/80J fractionated dosing described above.[22,24]

A 6-year clinical and histological follow-up of 53 BCCs, originally less than 3.5-mm thick, and treated by one or two sessions of ALA-PDT using the penetration enhancer dimethylsulphoxide and with prior lesion curettage, reported 81% of sites as disease free.[72]

PDT is a potentially useful option for patients with naevoid BCC syndrome (NBCCS), with series and cases reported and a large cohort of 33 patients treated by topical or systemic PDT, depending on whether lesions were less than/greater than 2 mm in thickness when assessed by ultrasound.[2,73] MAL-PDT for NBCCS can improve patient satisfaction and reduces the need for surgical procedures.[74]

Topical PDT is recommended for primary superficial and thin low-risk nodular BCC, but is a relatively poor choice for high-risk lesions including morphoeic BCC.[75] PDT is best considered for nodular lesions where surgical excision is relatively contraindicated, or where patient preference, reflecting past therapy history, comorbidities and/or cosmetic considerations result in a willingness to accept higher risk of recurrence. It is advised that patients receiving topical PDT for nodular BCC are reviewed for evidence of recurrence for at least 1 year.

© 2012 The Authors

Table 1: Treatment protocols for licensed indications

	Indication	Preparation/drug application	Illumination recommendations	Protocol	Reference
16.0% MAL Metvix® /Metvixia® (Galderma)	Thin, non-hyper keratotic AK (face/scalp), Bowens, superficial/ nodular BCC	Remove scales/crusts, slightly roughen surface (remove intact epidermis overlying nBCC) Apply a layer of cream approx 1-mm thick via spatula to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 h, then wipe clean with saline	After 3 h, remove dressing, wipe clean with saline, then illuminate using red light of spectrum 570–670 nm, total dose 75 J/cm^2 (red light with narrower spectrum can be used)	AK – one treatment, assess 3 months, BD and BCC – two sessions 7 days apart, reassess after 3 months. Remaining lesions may be retreated.	Full details @ http://www.medicines.org.uk/EMC/medicine/11913/SPC/Metvix+160 + mg+g+cream/ (accessed 24/12/11)
8 mg 5-ALA (2 mg/cm^2;) medicated plaster (Alacare®, Spirig AG)	Mild AK (≤1.8 cm in diameter) face/bald scalp (hairless areas)	Apply medicinal plaster up to a maximum of six patches on six different lesions. Incubate for 4 h.	After 4 h, remove plaster and expose to red light with a narrow spectrum device (spectrum of 630 ± 3 mm, total light dose of 37 J/cm^2).	Single use treatment, reassess after 3 months, retreat remaining lesions with alternative therapies.	Full details @ http://www.mhra.gov.uk /home/groups/par/documents /websiteresources /con057372.pdf (published 28.9.2009)
78 mg/g 5-ALA gel (Ameluz®; Biofrontera Bioscience)	Mild to moderate AK (Olsen 1 and 2), face /scalp	Remove scales/crusts, gently roughen surface, degrease skin. Apply a layer of cream approx 1-mm thick via spatula or protected fingertips to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 h, then wipe off remnant gel.	After 3 h, remove dressing, wipe clean, then illuminate using red light either with a narrow spectrum (~630 nm, light dose 37 J/cm^2;) or a broader, continuous spectrum (570–670 nm, light dose 75- 200 J/cm^2).	One treatment, reassess after 3 months, remaining lesions may be retreated.	Full details @ http://www.ema.europa.eu/ema /index.jsp?curl=pages/medicines /human/medicines/002204 /human_med_001528.jsp&mid =WC0b01ac058001d124 (published 09/01/2012)
20% ALA solution (Levulan Kerastick™; DUSA Pharmaceuticals)	Minimal /moderate thickness AK, face/scalp	Lesions should be clean and dry. Following solution admixture, apply directly to lesions by dabbing gently with the wet applicator tip, and reapply once dry. Treatment site not occluded, but protect from sun/bright light	After 14–18 h, 10 J/cm^2 light dose BLU-U (1000 s), positioning lamp as per manufacturer's instructions	One application and one dose of illumination per treatment site per 8-week treatment session	Full details @ http://www.dusapharma .com/levulan-product-information.html (accessed 24/12/11)

ALA, aminolaevulinic acid; AK, actinic keratoses; BCC, basal cell carcinomas; BD, Bowen's disease; MAL, methyl aminolaevulinate.

© 2012 The Authors

Adverse effects

Pain/burning sensation is often experienced during PDT, although varying widely in severity, usually developing within minutes of commencing light exposure and probably reflects nerve stimulation and/or tissue damage by reactive oxygen species, possibly aggravated by hyperthermia. Most patients tolerate PDT without anaesthesia, but pain is more likely to be experienced if large fields are treated, especially on well-innervated areas (face, scalp, hands, perineum), and is more common when treating AK than Bowen's/BCC.[76-79] Patients with sensitive skin types appear more prone to pain. The second treatment of a two-therapy cycle may be more painful.[80]

PDT with MAL has been stated to be less painful than ALA-PDT in comparison trials of scalp AK, although longer application time of ALA (5–6 h vs. 3 h) may have contributed[7,81] Greater pain was observed in comparison of ALA- with MAL-PDT in tape-stripped normal skin.[82] In a recent comparison of ALA and MAL in PDT for NMSC, both applied for 4 h, MAL-PDT was less painful on the head, but not on the trunk and extremities.[83] In a single-centre retrospective study comparing BP-200 ALA with MAL-PDT for AK, patients treated using MAL had a lower mean pain score and fewer treatment interruptions, although a similar level of pain was observed in a large randomized blinded comparison of BF-200 ALA with MAL for AK.[9,84]

The topical anaesthetics, tetracaine gel, a mixture of lignocaine 2.5% and prilocaine 2.5% or morphine gel, have not been shown to reduce pain significantly during PDT.[85–87] Cold-air analgesia, using a device to blow air at a temperature of −35°C, reduced pain duration and severity in a study of ALA-PDT for BD and BCC, although cooling may slow the photodynamic reaction.[88] Transcutaneous nerve stimulation appears to have limited effect.[89]

Nerve blocks are useful for large field treatments (e.g. forehead, entire scalp), more effective than cold-air analgesia in a split-face controlled study of MAL-PDT during treatment of multiple AK in the frontal region.[90–92]

PDT using low-intensity light (daylight, ambulatory) is less painful, but results in prolonged treatment times. PDT using a variable pulsed light was associated with reduced pain compared with standard red light MAL-PDT, whereas MAL-PDT using visible light plus water-filtered infrared A was equivalent in efficacy, but was almost painless.[93,94]

Erythema and oedema are common post-PDT, with erosion, crust formation and healing over 2–6 weeks, but ulceration is rare. Urtication of treatment sites has been described and is probably an exaggeration of the normal inflammatory response to PDT.[95] Following 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.[96,97] Postinflammatory hypo- and hyperpigmentation are rarely observed.[98] Hair loss is also possible, given concomitant sensitization of pilosebaceous units, but is more often observed with PDT for indurated BCC than AK.[99] A clinically obvious scar is rarely observed following PDT.

There is a risk of sensitization to MAL that might give an exaggerated response to patients receiving further PDT with the same drug formulation.[100–103]

Two case reports of melanoma within the field of previous PDT and of SCC developing following PDT (supplemented by topical 5-fluorouracil) for penile intraepithelial neoplasia could represent evidence of progression, but the melanomas may well have arisen coincidentally, and the SCC development may be due to incomplete response of the PIN to two therapy modalities.[104-106]

References

1 Braathen LR, Szeimies RM, Basset Seguin N *et al.* Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. *J Am Acad Dermatol* 2007; **56**: 125–143.
2 Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy. *Br J Dermatol* 2008; **159**: 1245–1266.
3 Morton CA, Szeimies RM, Sideroff A, Braathen LR. European guidelines for photodynamic therapy part 2: emerging indications. *J Eur Acad Dermatol Venereol* 2012; doi: 10.1111/jdv.12026 [Epub ahead of print].
4 Kennedy J C, Pottier R H, Pross D C. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol, B* 1990; **6**: 143–148.
5 Henderson BW, Dougherty TJ. How does photodynamic therapy work?. *Photochem Photobiol* 1992; **55**: 145–157.
6 Babilas P, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology. *Eur J Dermatol* 2006; **16**: 340–348.
7 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.
8 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**: 642–645.
9 Dirschka T, Radny P, Dominicus R *et al.* Photodynamic therapy with BF-200 ALA for the treatment of actinic keratoses: results of a multicentre, randomized, observer-blind phase III study in comparison with registered methyl-5-aminolaevulinate cream and placebo. *Br J Dermatol* 2012; **166**: 137–146.
10 Hauschild A, Stockfleth E, Popp G *et al.* Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. *Br J Dermatol* 2009; **160**: 1066–1074.
11 Gerritsen MJP, Smits T, Kleinpenning MM *et al.* Pretreatment to enhance protoporphyrin IX accumulation in photodynamic therapy. *Dermatology*, 2009; **218**: 193–202.
12 Rhodes LE, de Rie M, Enstrom 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.
13 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**: 140–154.
14 Braathen L R, Paredes B E, Saksela O *et al.* Short incubation with methyl aminolevulinate for photodynamic therapy of actinic keratoses. *J Eur Acad Dermatol Venereol* 2009; **23**: 550–555.
15 Kacerovska D, Pizinger K, Majer F *et al.* Photodynamic therapy of nonmelanoma skin cancer with topical hypericum perforatum extract–a pilot study. *Photochem Photobiol* 2008; **84**: 779–785.

© 2012 The Authors
Journal of the European Academy of Dermatology and Venereology © 2012 European Academy of Dermatology and Venereology

16 Rook AH, Wood GS, Duvic M *et al.* A phase II placebo-controlled study of photodynamic therapy with topical hypericin and visible light irradiation in the treatment of cutaneous T-cell lymphoma and psoriasis. *J Am Acad Dermatol* 2010; **63**: 984–990.
17 Baron ED, Malbasa CL, Santo-Domingo D *et al.* Silicon phthalocyanine (Pc 4) photodynamic therapy is a safe modality for cutaneous neoplasms: results of a phase 1 clinical trial. *Lasers Surg Med* 2010; **42**: 728–735.
18 Maisch T, Moor AC, Regensburger J *et al.* Intense pulse light and 5-ALA PDT: phototoxic effects in vitro depend on the spectral overlap with protoporphyrine IX but do not match cut-off filter notations. *Lasers Surg Med* 2011; **43**: 176–182.
19 Szeimies RM, Radny P, Sebastian M *et al.* Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. *Br J Dermatol* 2010; **163**: 386–394.
20 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**: 2679–2686.
21 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**: 264–265.
22 de Haas ER, de Vijlder HC, Sterenborg HJ *et al.* Fractionated aminolevulinic acid-photodynamic therapy provides additional evidence for the use of PDT for non-melanoma skin cancer. *J Eur Acad Dermatol Venereol* 2008; **22**: 426–430.
23 Sotiriou E, Apalla Z, Chovarda E *et al.* Single vs. fractionated photodynamic therapy for face and scalp actinic keratoses: a randomized, intraindividual comparison trial with 12 month follow-up. *J Eur Acad Dermatol Venereol* 2012; **26**: 36–40.
24 Mosterd K, Thissen MRTM, Nelemans P *et al.* Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. *Br J Dermatol* 2008; **159**: 864–870.
25 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-blind study. *Br J Dermatol* 2008; **158**: 740–746.
26 Wiegell SR, Fabricius S, Stender I M *et al.* A randomized, multicentre study of directed daylight exposure times of 1 1/2 vs. 2 1/2 h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. *Br J Dermatol* 2011; **164**: 1083–1090.
27 Wiegell SR, Fabricius S, Gniadecka M *et al.* Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp - a randomized multicentre study. *Br J Dermatol* 2012; **166**: 1327–1332.
28 Wiegell S, Wulf H, Szeimies R.-.M *et al.*, Daylight photodynamic therapy for actinic keratosis: an international consensus. *J Eur Acad Dermatol Venereol* 2012; *Br J Dermatol* 2012; **26**: 673–679.
29 Moseley H, Allen JW, Ibbotson S *et al.* Ambulatory photodynamic therapy: a new concept in delivering photodynamic therapy. *Br J Dermatol* 2006; **154**: 747–750.
30 Attili SK, Lesar A, McNeill A *et al.* An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer. *Br J Dermatol* 2009; **161**: 170–173.
31 Moseley H, Brancaleon L, Lesar AE, Ferguson J, Ibbotson SH. Does surface preparation alter ALA uptake in superficial non-melanoma skin cancer in vivo? *Photodermatol Photoimmunol Photomed*. 2008; **24**: 72–75.
32 Szeimies RM, Stockfleth E, Popp G *et al.* Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. *Br J Dermatol* 2010; **162**: 410–414.
33 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**: 338–339.
34 Clementoni MT, B-Roscher M, Munavalli GS. Photodynamic photorejuvenation of the face with a combination of microneedling red light and broadband pulsed light. *Lasers Surg Med* 2010; **42**: 150–159.
35 Whitaker IS, Shokrollahi K, James W *et al.* Combined CO_2 Laser With Photodynamic Therapy for the Treatment of Nodular Basal Cell Carcinomas. *Ann Plast Surg* 2007; **59**: 484–488.
36 Togsverd-Bo K, Haak CS, Thaysen-Petersen D, Wulf HC, Anderson RR, Hædersdal M. Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser – a randomized clinical trial. *Br J Dermatol* 2012; **166**: 1262–1269.
37 Fritsch CJ, Ruzicka T. Fluorescence diagnosis and photodynamic therapy in dermatology from experimental state to clinic standard methods. *J Environ Pathol Toxicol Oncol* 2006; **25**: 425–439.
38 Tyrrell J, Campbell S, Curnow A. Validation of a non-invasive fluorescence imaging system to monitor dermatological PDT. *Photodiagnosis Photodyn Ther* 2010; **7**: 86–97.
39 Lee CY, Kim KH, Kim YH. The efficacy of photodynamic therapy in defining the lateral border between a tumour and a tumour-free area during Mohs micrographic surgery*Dermatol Surg*. 2010; **36**: 1704–1710.
40 Neus S, Gambichler T, Bechara FG, Wohl S, Lehmann P. Preoperative assessment of basal cell carcinoma using conventional fluorescence diagnosis. *Arch Dermatol Res* 2009; **301**: 289–94.
41 Tyrrell JS, Campbell SM, Curnow A. The relationship between protoporphyrin IX photobleaching during real-time dermatological methyl-aminolevulinate photodynamic therapy (MAL-PDT) and subsequent clinical outcome. *Lasers Surg Med* 2010; **42**: 613–619.
42 Smits T, Kleinpenning MM, Blokx WAM, van de Kerkhof PCM, van Erp PEJ, Gerritsen M-JP. Fluorescence diagnosis in keratinocytic intraepidermal neoplasias. *J Am Acad Dermatol* 2007; **57**: 824–831.
43 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**: 727–733.
44 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**: 41–46.
45 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* 2005; **85**: 424–428.
46 Morton C, 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**: 1029–1036. Morton CA. Guidelines for topical photodynamic therapy 2008
47 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.
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**: 994–999.
49 Sotiriou E, Apalla Z, Maliamani F *et al.* Intraindividual, right–left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol* 2009; **23**: 1061–1065.
50 Sotiriou E, Apalla Z, Chovarda E, Panagiotidou D, Ioannides D. Photodynamic therapy with 5-aminolevulinic acid in actinic cheilitis: an

© 2012 The Authors

18 month clinical and histological follow-up. *J Eur Acad Dermatol Venereol* 2010; **24**: 916–920.
51 Berking C, Herzinger T, Flaig MJ *et al.* The efficacy of photodynamic therapy in actinic chielitis of the lower lip: a prospective study of 15 patients. *Dermatol Surg* 2007; **33**: 825–830.
52 Sotiriou E, Lallas A, Gooussi C *et al.* Sequential use of photodynamic therapy and imiquimod 5% cream for the treatment of actinic cheilitis; a 12 month follow-up study. *Br J Dermatol* 2011; **165**: 888–892.
53 Stockfleth E, Terhorst D, Braathen L. *et al.* Guidelines on actinic keratosis. European Dermatology Forum: http://www.euroderm.org/edf/images/stories/guidelines/guideline_Management_Actinic_Keratoses-update2011.pdf.
54 De Berker D, Mc Gregor J, Hughes B. Guidelines for the management of actinic keratosis. *Br J Dermatol* 2007; **156**: 222–230.
55 Serra-Guillen C, Nagore E, Hueso L *et al.* A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate. *Br J Dermatol* 2011; **164**: 429–433.
56 Morton CA, Horn M, Leman J *et al.* A randomized, placebo-controlled, European study comparing MAL-PDT with cryotherapy and 5-fluorouracil in subjects with Bowen's disease. *Arch Dermatol* 2006; **142**: 729–735.
57 Calzavara-Pinton P, Venturini M, Sala R. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. *Br J Dermatol* 2008; **159**: 137–144.
58 Truchuelo M, Fernández-Guarino M, Fleta B, Alcántara J, Jaén P. Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions. *J Eur Acad Dermatol Venereol* 2012; **26**: 868–874.
59 Lopez N, Meyer-Gonzalez T, Herrera-Acosta E *et al.* Photodynamic therapy in the treatment of extensive Bowen's disease. *J Dermatolog Treat* 2011. doi: 10.3109/09546634.2011.590789. [Epub ahead of print].
60 Paoli J, Ternesten Bratel A, Lowhagen G-B *et al.* Penile intraepithelial neoplasia: results of photodynamic therapy. *Acta Derm Venereol* 2006; **86**: 418–421.
61 Cox N, Eedy D, Morton C. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol* 2007; **156**: 11–21.
62 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**: 547–553.
63 Szeimies R, Ibbotson S, Murrell D *et al.* A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20mm), with a 12-month follow-up. *J Eur Acad Dermatol Venereol* 2008; **22**: 1302–1311.
64 Peng Q, Warloe T, Berg K *et al.* 5-Aminolevulinic acid-based photodynamic therapy: Clinical research and future challenges. *Cancer* 1997; **79**: 2282–2308.
65 Morton CA, Whitehurst C, McColl JH, Moore JV, MacKie RM. Photodynamic therapy for basal cell carcinoma - Effect of tumour thickness and duration of photosensitiser application on response. *Arch Dermatol* 1998; **134**: 248–249.
66 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**: 765–772.
67 Rhodes LE, de Rie MA, Leifsdottir R *et al.* Five year follow up of a randomized prospective trial of topical methyl aminolevulinate-photodynamic therapy versus surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; **143**: 1131–1136.
68 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**: 832–840.
69 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 BCC. *Br J Dermatol* 2007; **157**: 401–403.
70 Foley P, Freeman M, Menter A *et al.* Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies. *Int J Dermatol* 2009; **48**: 1236–1245.
71 Fantini F, Greco A, Del Giovane C *et al.* Photodynamic therapy for basal cell carcinoma: clinical and pathological determinants of response. *J Eur Acad Dermatol Venereol* 2011; **25**: 896–901.
72 Christensen E, Skogvoll E, Viset T, Warloe T, Sundstrøm S. Photodynamic therapy with 5-aminolaevulinic acid, dimethylsulfoxide and curettage in basal cell carcinoma: a 6-year clinical and histological follow-up. *J Eur Acad Dermatol Venereol* 2009; **23**: 58–66.
73 Loncaster J, Swindell R, Slevin F *et al.* Efficacy of photodynamic therapy as a treatment for Gorlin Syndrome-related basal cell carcinomas. *Clin Oncol (R Coll Radiol)* 2009; **21**: 502–508.
74 Pauwels C, Mazereeuw-Hautier J, Basset-Seguin N *et al.* Topical methyl aminolevulinate photodynamic therapy for management of basal cell carcinomas in patients with basal cell nevus syndrome improves patient's satisfaction and reduces the need for surgical procedures. *J Eur Acad Dermatol Venereol* 2011; **25**: 861–864.
75 Telfer N, Colver G, Morton C. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; **159**: 35–48.
76 Grapengiesser S, Ericson M, Gudmundsson F *et al.* Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol* 2002; **27**: 493–497.
77 Sandberg C, Stenquist B, Rosdahl I *et al.* Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Derm Venereol* 2006; **86**: 404–408.
78 Warren CB, Karai LJ, Vidmos A, Maytin EV. Pain associated with aminolevulinic acid-photodynamic therapy of skin disease. *J Am Acad Dermatol* 2009; **61**: 1033–1043.
79 Halldin CB, Gillstedt M, Paoli J *et al.* Predictors of pain associated with photodynamic therapy: a retrospective study of 658 treatments. *Acta Derm Venereol* 2011; **91**: 545–551.
80 Arits A, Van De Weert M, Nelemans P, Kelleners-Smeets N. Pain during topical photodynamic therapy: uncomfortable and unpredictable. *J Eur Acad Dermatol Venereol* 2010; **24**: 1452–1457.
81 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**: 353–356.
82 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**: 1173–1177.
83 Gaal M, Otrosinka S, Baltas E *et al.* Photodynamic therapy of non-melanoma skin cancer with methyl aminolavulinate is associated with less pain than with aminolaevulinic acid. *Acta Derm Venereol* 2012; **92**: 173–175.
84 Gholam P, Weberschock T, Denk K, Enk A. Treatment with 5-aminolaevulinic acid methylester is less painful than treatment with 5-aminolaevulinic acid nanoemulsion in topical photodynamic therapy for actinic keratosis. *Dermatology* 2011; **222**: 358–362.
85 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**: 337–340.
86 Langan SM, Collins P. Randomized, double-blind, placebo-controlled prospective study of the efficacy of topical anaesthesia with a eutetic 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**: 146–149.
87 Skiveren J, Haedersdal M, Philipsen PA *et al.* Morphine gel 0.3% does not relieve pain during topical photodynamic therapy: a randomized

© 2012 The Authors

double-blind, placebo controlled study. *Acta Derm Venereol* 2006; **86**: 409–411.
88 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**: 63–66.
89 Halldin CB, Paoli J, Sandberg C *et al.* Transcutaneous electrical nerve stimulation for pain relief during photodynamic therapy of actinic keratosis. *Acta Derm Venereol* 2008; **88**: 311–313.
90 Paoli J, Halldin C, Ericson MB, Wennberg AM. Nerve blocks provide effective pain relief during photodynamic therapy for extensive facial actinic keratoses. *Clin Exp Dermatol* 2008; **33**: 559–564.
91 Halldin CB, Paoli J, Sandberg C, Gonzalez H, Wennberg AM. Nerve blocks enable adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp. *Br J Dermatol* 2009; **160**: 795–800.
92 Serra-Guillen C, Hueso L, Nagore E *et al.* Comparative study between cold air analgesia and supraorbital and supratrochlear nerve block for the management of pain during photodynamic therapy for actinic keratoses of the frontotemporal zone. *Br J Dermatol* 2009; **161**: 353–356.
93 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 contrommed trial. *Br J Dermatol* 2007; **157**: 111–117.
94 Von Felbert V, Hoffmann G, Hoff-Lesch S *et al.* Photodynamic therapy of multiple actinic keratoses: reduced pain through use of visible light plus water-filtered infrared A compared with light from light-emitting diodes. *Br J Dermatol* 2010; **163**: 607–615.
95 Kerr AC, Ferguson J, Ibbotson SH. Acute phototoxicity with urticarial reatures during topical 5-aminolaevulinic acid photodynamic therapy. *Clin Exp Dermatol* 2007; **32**: 210–212.
96 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**: 112–122.
97 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**: 301–307.
98 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**: 403–416.
99 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**: 319–324.
100 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**: 143–145.
101 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**: 35–36.
102 Hohwy T, Andersen KE, Solvsten H, Sommerlund M. Allergic contact dermatitis to methyl aminolevulinate after photodynamic therapy in 9 patients. *Contact Derm* 2007; **57**: 321–323.
103 Korshoj S, Solvsten H, Erlandsen M, Sommerlund M. Frequency of sensitization to methyl aminolaevulinate after photodynamic therapy. *Contact Derm* 2009; **60**: 320–324.
104 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**: 53–54.
105 Schreml S, Gantner S, Steinbauer J. *et al.* Melanoma promotion after photodynamic therapy of a suspected Bowen's disease lesion. *Dermatology* 2009; **219**: 279–281.
106 Varma S, Holt P, Anstey A. Erythroplasia of Queyrat treated by topical amino-laevulinic acid photodynamic therapy: a cautionary tale. *Br J Dermatol* 2000; **142**: 825–826.

Appendix I

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 II

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 randomisation
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).

© 2012 The Authors
Journal of the European Academy of Dermatology and Venereology © 2012 European Academy of Dermatology and Venereology

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. Braathen[4]

[1]Department of Dermatology, Stirling Community Hospital, Stirling, UK
[2]Klinik für Dermatologie und Allergologie, Klinikum Vest GmbH, Behandlungszentrum, Knappschaftskrankenhaus Recklinghausen, Recklinghausen, Germany
[3]Department of Dermatology and Venereology, Medical University of Innsbruck, Austria
[4]Department 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.

Received: 27 June 2012; Accepted: 03 October 2012

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 clinincal trials from Almirall, Biofrontera, Galderma, Leo, photonamic and Spirig. The other authors declare no conflicts of interest.

[Correction added on 30 November 2012, after first online publication: conflict of interest statement was amended.]

Funding sources

None declared.

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

© 2012 The Authors
Journal of the European Academy of Dermatology and Venereology © 2012 European Academy of Dermatology and Venereology

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 intrapatient 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 intrapatient 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 intrapatient 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 multilocular 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-

© 2012 The Authors

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/cm^2 600–700 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/cm^2 550–700 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/cm^2 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

© 2012 The Authors

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 accuminata 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. CO_2 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 CO_2-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 CO_2-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 parisotological 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 lentigines 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

© 2012 The Authors

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).

© 2012 The Authors

References

1 Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for photodynamic therapy part 1: current indications. *J Eur Acad Dermatol Venereol* 2012; doi: 10.1111/jdv.12031 [Epub ahead of print].

2 Braathen Lasse R, Szeimies Rolf M, Basset Seguin N *et al.* Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *J Am Acad Dermatol* 2007; **56**: 125–143.

3 Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy. *Br J Dermatol* 2008; **159**: 1245–1266.

4 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**: 542–544.

5 Jang MS, Doh KS, Kang JS *et al.* A comparative split-face study of photodynamic therapy with indocyanine green and indole-3-acetic acid for the treatment of acne vulgaris. *Br J Dermatol* 2011; **165**: 1095–1100.

6 Wiegell S, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006; **54**: 647–651.

7 Stender I-M, Borgbjerg F, Molke Villumsen J, Lock-Andersen J, Wulf H-C. Pain induced by photodynamic therapy of warts. *Photodermatol Photoimmunol Photomed* 2006; **22**: 304–309.

8 Dragieva G, Prinz BM, Hafner J *et al.* A randomised 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.

9 Piaserico S, Belloni Fortina A, Rigotti P *et al.* Topical photodynamic therapy of actinic keratosis in renal transplant patients. *Transplant Proc* 2007; **39**: 1847–1850.

10 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**: 279–284.

11 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**: 115–121.

12 Perrett CM, McGregor JM, Warwick J *et al.* Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil and topical photodynamic therapy. *Br J Dermatol* 2007; **156**: 320–328.

13 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* 2006; **86**: 25–28.

14 Wennberg AM, Stenquist B, Stockfleth E *et al.* Photodynamic therapy with methyl aminolevulinate for prevention of new lesions in transplant recipients: a randomized study. *Transplantation* 2008; **86**: 423–429.

15 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**: 569–574.

16 Willey A, Mehta S, Lee PK. Reduction in incidence of squamous cell carcinoma in solid organ transplant recipients treated by cyclic Photodynamic therapy. *Dermatol Surg* 2010; **36**: 652–658.

17 Braathen L., Morton C., Basset-Seguin N *et al.*. Photodynamic therapy for skin field cancerization: an international consensus. International Society for Photodynamic Therapy in Dermatology. *J Eur Acad Dermatol Venereol* 2012; **26**: 1063–1066.

18 Basset-Seguin N, Baumann Conzett K, Gerritsen MJP *et al.*. Photodynamic therapy for actinic keratoses in organ transplant recipients. *J Eur Acad Dermatol Venereol* 2012; DOI: 10.1111/J.1468-3083.2011.04356.

19 Apalla Z, Sotiriou E, Chovarda E, Lefaki I, Devliotou-Panagiotidou D, Ioannides D. Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. *Br J Dermatol* 2010; **162**: 171–175.

20 Bagazgoitia L, Cuevas Santos J, Juarranz A, Jaen P. Photodynamic therapy reduces the histologic features of actinic damage and the expression of early oncogenic markers. *Br J Dermatol* 2011; **165**: 144–145.

21 Szeimies RM, Torezan L, Niwa A *et al.*. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. *Br J Dermatol* 2012; **167**: 150–159 DOI: 10.1111/j.1365-2133.2012.10887.x

22 Zane C, Venturini M, Sala R, Calzavara-Pinton P. Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed* 2006; **22**: 254–258.

23 Edstrom DW, Porwit A, Ros AM. Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: clinical and histological response. *Acta Derm Venereol* 2001; **81**: 184–188.

24 Debu A, Girard C, Kluger N, Guillot B, Dereure O. Topical methyl aminolaevulinate photodynamic therapy in erosive facial mycosis fungoides. *Br J Dermatol* 2010; **163**: 884–885.

25 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**: 524–526.

26 Shieh S, Dee AS, Cheney RT *et al.* Photodynamic therapy for the treatment of extramammary Paget's disease. *Br J Dermatol* 2002; **146**: 1000–1005.

27 Mikasa K, Watananabe 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.

28 Rapagliesi F, Fontanelli R, Rossi G *et al.* Photodynamic therapy using a methyl ester of 5-aminolaevulinic acid in recurrent Paget's disease of the vulva: a pilot study. *Gynecol Oncol* 2006; **103**: 581–586.

29 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**: 1143–1145.

30 Sakamoto FH, Lopes JD, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice Part 1 Acne: when and why consider photodynamic therapy? *J Am Acad Dermatol* 2010; **63**: 183–193.

31 Ramstad S, Futsaether CM, Johnsson A. Porphyrin sensitization and intracellular calcium changes in the prokaryote, propionibacterium acnes. *J Photochem Photobiol, B* 1997; **40**: 141–148.

32 Sakamoto FH, Torezan L, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice Part 2 Understanding parameters for acne treatment with photodynamic therapy. *J Am Acad Dermatol* 2010; **63**: 195–211.

33 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**: 140–154.

34 Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol* 2006; **154**: 969–976.

35 Horfelt 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**: 608–613.

36 Mavilia L, Malara G, Moretti G *et al.* Photodynamic therapy of acne using methyl aminolevulinate diluted to 4% together with low doses of red light. *Br J Dermatol* 2007; **157**: 810–811.

37 de Leeuw J, van der Beek N, Bjerring P, Neumann HAM. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid 0.5% liposomal spray and intense pulsed light in combination with topical keratolytic agents. *J Eur Acad Dermatol Venereol* 2010; **24**: 460–469.

38 Horn M, Wolf P. Topical methyl aminolevulinate photodynamic therapy for the treatment of folliculitis. *Photodermatol Photoimmunol Photomed* 2007; **23**: 145–147.

© 2012 The Authors

39 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**: 1274–1276.
40 Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. *J Drugs Dermatol* 2003; **2**: 501–504.
41 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; **6**(Suppl): S6–S9.
42 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**: 781–782.
43 Gold MH, Bridges NM, Bradshaw VL, Boring M. ALA-PDT and blue light therapy for hidradenitis suppurativa. *J Drugs Dermatol* 2004; **3**: S32–S35.
44 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**: 803–804.
45 Bryld LE, Jemec GBE. Photodynamic therapy in a series of rosacea patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 1199–1202.
46 Togsverd-Bo K, Wiegell SR, Wulf HC, Haedersdal M. Short and limited effect of long-pulsed dye laser alone and in combination with photodynamic therapy for inflammatory rosacea. *J Eur Acad Dermatol Venereol* 2008; **23**: 200–201.
47 Stender I M, Na R, Fogh H, Gluud C, Wulf H C. Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. *Lancet* 2000; **355**: 963–966.
48 Stender I.M, Lock-Andersen J, Wulf HC. Recalcitrant hand and foot warts successfully treated with photodynamic therapy with topical 5-aminolaevulinic acid: a pilot study. *Clin Exp Dermatol* 1999; **24**: 154–159.
49 Smucler R, Jatsova 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**: 51–53.
50 Mizuki D, Kaneko T, Hanada K. Successful treatment of topical photodynamic therapy using 5-aminolevulinic acid for plane warts. *Br J Dermatol* 2003; **149**: 1087–1088.
51 Lu YG, Wu JJ, He Y, Yang HZ, Yang YD. Efficacy of topical aminolaevulinic acid photodynamic therapy for the treatment of verruca planae. *Photomed Laser Surg* 2010; **28**: 651–653.
52 Schroeter CA, Kaas L, Waterval JJ, Bos PM, Neumann HAM. Successful treatment of periingual warts using photodynamic therapy: a pilot study. *J Eur Acad Dermatol Venereol* 2007; **21**: 1170–1174.
53 Chiong W-S, Kang GYM. Dramatic clearance of a recalcitrant acral wart using methyl aminolevulinate-red light photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2009; **25**: 225–226.
54 Fehr MK, Hornung P, Schwarz VA *et al.* Photodynamic therapy of vulvar and vaginal condylomata and intraepithelial neoplasia using topical 5-aminolaevulinic acid. *Lasers Surg Med* 2002; **30**: 273–279.
55 Stefanaki IM, Georgiou S, Themelis GC *et al. In vivo* fluorescence kinetics and photodynamic therapy in condylomata acuminata. *Br J Dermatol* 2003; **149**: 972–976.
56 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**: 880–885.
57 Chen K, Chang BZ, Ju M *et al.* Comparative study of photodynamic therapy vs. CO2 laser vaporization in treatment of condylomata acuminate, a randomized clinical trial. *Br J Dermatol* 2007; **156**: 516–520.
58 Liang J, Lu XN, Tang H, Zhang Z, Fan J, Xu JH. Evaluation of photodynamic therapy using topical aminolaevulinic acid hydrochloride in the treatment of condyloma acuminate: a comparative, randomized clinical trial. *Photodermatol Photoimmunol Photomed* 2009; **25**: 293–297.
59 Szeimies RM, Schleyer V, Moll I *et al.* Adjuvant photodynamic therapy does not prevent recurrence of condylomata acuminata after carbon dioxide laser ablation-A phase III, prospective, randomized, bicentric, double-blind study. *Dermatol Surg* 2009; **35**: 757–764.
60 van der Snoek EM, Robinson DJ, van Hellemond JJ, Neumann HAM. A review of photodynamic therapy in cutaneous leishmaniasis. *J Eur Acad Dermatol Venereol* 2008; **22**: 918–922.
61 Enk CD, Fritsch C, Jonas F *et al.* Treatment of cutaneous leishmaniasis with photodynamic therapy. *Arch Dermatol* 2003; **139**: 432–434.
62 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**: 634–637.
63 Akilov OE, Kosaka S, O'Riordan K, Hasan T. A mechanistic study of delta-aminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis. *J Invest Dermatol* 2007; **127**: 1546–1549.
64 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**: 543–551.
65 Kohl E, Torezan LAR, Landthaler M, Szeimies RM. Aesthetic effects of topical photodynamic therapy. *J Eur Acad Dermatol Venereol* 2010; **24**: 1261–1269.
66 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**: 1247–1252.
67 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.
68 Key DJ. Aminolaevulinic acid-pulsed dye laser photodynamic therapy for the treatment of photoaging. *Cosmet Dermatol* 2005; **18**: 31–36.
69 Ruiz-Rodriguez R, Lopez L, Candelas D, Pedraz J. Photorejuvenation using topical 5-methyl aminolevulinate and red light. *J Drugs Dermatol* 2008; **7**: 633–637.
70 Ruiz-Rodriguez R, Lopez L, Candelas D, Zelickson B. Enhanced efficacy photodynamic therapy after fractional resurfacing: fractional photodynamic rejuvenation. *J Drugs Dermatol* 2007; **6**: 818–820.
71 Sanclemente G, Medina L, Villa J-F, Barrera L-M, Garcia H-I. A prospective split-face double-blind randomized placebo-controlled trial to assess the efficacy of methyl aminolevulinate + red-light in patients with facial photodamage. *J Eur Acad Dermatol Venereol* 2011; **25**: 49–58.
72 Karrer S, Abels C, Landthaler M, Szeimies R-M. Topical photodynamic therapy for localized scleroderma. *Acta Derm Venereol* 2000; **80**: 26–27.
73 Karrer S, Bosserhoff AK, Weiderer P *et al.* Influence of 5-amino-levulinic acid and red light on collagen metabolism of human dermal fibroblasts. *J Invest Dermatol* 2003; **120**: 325–331.
74 Zawislak AA, McCluggage WG, Donnelly RF *et al.* Response of vulval lichen sclerosus and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolaevulinic acid from a novel bioadhesive patch system. *Photodermatol Photoimmunol Photomed* 2009; **25**: 111–113.
75 Hillemanns P, Untch M, Prove F *et al.* Photodynamic therapy of vulvar lichen sclerosus with 5-aminolaevulinic acid. *Obstet Gynecol* 1999; **93**: 71–74.
76 Exadaktylou D, Kurwa HA, Calonje E, Barlow RJ. Treatment of Darier's disease with photodynamic therapy. *Br J Dermatol* 2003; **149**: 606–610.
77 Richey DF, Hopson B. Photodynamic therapy for perioral dermatitis. *J Drugs Dermatol* 2006; **5**: 12–16.
78 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**: 394–395.
79 Gilaberte Y, Frias MP, Perez-Lorenz JB. Chondrodermatitis nodularis helicis successfully treated with photodynamic therapy. *Arch Dermatol* 2010; **146**: 1080–1082.

© 2012 The Authors

80 Moiin A. Photodynamic therapy for molluscum contagiosum infection in HIV-co-infected patients: review of 6 patients. *J Drugs Dermatol* 2003; **2**: 637–639.
81 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**: 144–147.
82 Sotiriou E, Koussidou T, Patsatsi A, Apalla Z, Ionnides D. 5-aminolevulinic acid-photodynamic therapy treatment for dermatophyte tinea pedis of interdigitate type: a small clinical study. *J Eur Acad Dermatol Venereol* 2009; **23**: 203–204.
83 Sotiriou E, Panagiotidou D, Ionnides D. 5-aminolevulinic acid-photodynamic therapy treatment for tinea cruris caused by Trychophyton rubrum: report of 10 cases. *J Eur Acad Dermatol Venereol* 2009; **23**: 341–342.
84 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**: 823–828.
85 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**: 560–562.
86 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**: 279–283.
87 Campbell SM, Tyrrell J, Marshall R, Curnow A. Effect of MAL-photodynamic therapy on hypertrophic scarring. *Photodiagn Photodyn Ther* 2010; **7**: 183–188.
88 Sakamoto F, Izikson L, Tannous Z, Zurakowski D, Anderson RR. Surgical scar remodelling after photodynamic therapy using aminolaevulinic acid or its methylester: a retrospective, blinded study of patients with field cancerization. *Br J Dermatol* 2012; **166**: 413–416.
89 Caekelbergh K, Annemans L, Lambert J, Roelands R. Economic evaluation of methyl aminolevulinate photodynamic therapy in the management of actinic keratoses and basal cell carcinoma. *Br J Dermatol* 2006; **155**: 784–790.
90 Annemans L, Caekelbergh K, Roelandts R, *et al.* Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. *Euro J Dermatol* 2008; **18**: 539–546.
91 Aguilar M, De Troya M, Martin L, Benítez N, González M. A cost analysis of photodynamic therapy with methyl aminolevulinate and imiquimod compared with conventional surgery for the treatment of superficial basal cell carcinoma and Bowen's disease of the lower extremities. *J Eur Acad Dermatol Venereol* 2010; **24**: 1431–1436.
92 Wilson ECF. Cost effectiveness of imiquimod 5% cream compared with methyl aminolevulinate-based photodynamic therapy in the treatment of non-hyperkeratotic, non-hypertrophic actinic (solar) keratoses: a decision tree model. *Pharmacoeconomics* 2010; **28**: 1055–1064.
93 Muston D, Downs A, Rives V. An economic evaluation of topical treatments for actinic keratosis. *J Dermatolog Treat* 2009; **20**: 1–10.

© 2012 The Authors
Journal of the European Academy of Dermatology and Venereology © 2012 European Academy of Dermatology and Venereology