




## GUIDELINES

# European Dermatology Forum guidelines on topical photodynamic therapy 2019 Part 1: treatment delivery and established indications – actinic keratoses, Bowen's disease and basal cell carcinomas

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## Abstract

Topical photodynamic therapy (PDT) is a widely approved therapy for actinic keratoses, Bowen's disease (squamous cell carcinoma *in situ*), superficial and certain thin basal cell carcinomas. Recurrence rates when standard treatment protocols are used are typically equivalent to existing therapies, although inferior to surgery for nodular basal cell carcinoma. PDT can be used both as lesional and field therapies and has the potential to delay/reduce the development of new lesions. A protocol using daylight to treat actinic keratoses is widely practised, with conventional PDT using a red light after typically a 3-h period of occlusion employed for other superficial skin cancer indications as well as for actinic keratoses when daylight therapy is not feasible. PDT is a well-tolerated therapy although discomfort associated with conventional protocol may require pain-reduction measures. PDT using daylight is associated with no or minimal pain and preferred by patient. There is an emerging literature on enhancing conventional PDT protocols or combined PDT with another treatment to increase response rates. This guideline, published over two parts, considers all current approved and emerging indications for the use of topical PDT in dermatology, prepared by the PDT subgroup of the European Dermatology Forum guidelines committee. It presents consensual expert recommendations reflecting current published evidence.

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Forms submitted.

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## Introduction

This updated guideline seeks to promote safe and effective practice across Europe in the delivery of topical photodynamic therapy (PDT) in dermatological indications and reflects evidence derived from a systematic literature review and previous PDT and disease-specific therapy guidelines.<sup>1–6</sup> Recommendations concerning emerging indications for topical PDT are reviewed in Part II.<sup>7</sup>

Photodynamic therapy involves the activation of a photosensitizing drug by visible light to produce reactive oxygen species within target cells, resulting in their destruction with additional immune-modulatory effects observed.<sup>8</sup> In dermatological indications, PDT is usually performed by topical application of precursors of the haeme biosynthetic pathway, in particular 5-aminolaevulinic acid (5-ALA) or its ester, methyl aminolaevulinic acid (MAL), converted within target cells into photoactivatable porphyrins, especially protoporphyrin IX (PpIX). After an incubation period, light of an appropriate wavelength activates the photosensitizer promoting the photodynamic reaction. Before light illumination, it is possible to detect skin surface fluorescence, assisting detection and delineation of both visible and incipient lesions.

Three agents are currently licensed for use in Europe (Table 1): MAL (160 mg/g) Metvix®/Metvixia® (Galderma, Paris, France) is used along with red light to treat non-hyperkeratotic actinic keratosis (AK), squamous cell carcinoma *in situ* (SCC *in situ*/Bowen's disease), superficial and nodular basal cell carcinomas (sBCC, nBCC), although approvals vary between countries. A nanoemulsion of 5-ALA (Ameluz®; Biofrontera AG, Leverkusen, Germany) is licensed for PDT in combination with red light for the treatment of mild and moderate AK, field cancerization, and superficial and low-risk nodular BCC. A patch containing 5-ALA (Alacare®; Photonamic, Pinneberg, Germany) is approved for the treatment of mild AK in a single treatment session in combination with red light without pretreatment of the lesion. A 20% formulation of 5-ALA, Levulan (DUSA Pharmaceuticals, Wilmington, MA, USA), is approved in N. 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 ALA made in hospital pharmacies, so direct comparison of early studies may not be valid.

Treatment is generally well tolerated but discomfort or pain is common during conventional PDT. Alterations in the way PDT are delivered, including the use of daylight or shorter photosensitizer application times, are associated with decreased discomfort, with licence approvals for daylight PDT for actinic keratoses using the MAL and nanoemulsion ALA.

## Method of action

### Photosensitizers

Aminolaevulinic acid is hydrophilic whilst 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, nodular BCC or acne, failed to show a difference in response with the formulation of ALA used.<sup>9–11</sup> More recently, a nanoemulsion of ALA (Ameluz®), which improves ALA stability and skin penetration, has achieved significantly higher clearance of patients with AK when compared with MAL.<sup>12</sup> A self-adhesive 5-ALA patch (Alacare®), directly applied to AK without the need of lesion preparation, has been shown to be superior to cryotherapy for mild and moderate thickness AK, providing a clean and uniform method of photosensitizer application.<sup>13</sup>

Enhancing photosensitizer penetration may increase the efficacy of PDT, but currently there is no licensed approval for a protocol that uses a penetration enhancer or iontophoresis. Elevating skin temperature during ALA application may also improve efficacy as PpIX production is a temperature-dependant process.<sup>14</sup>

In nodular BCC of up to 2 mm thickness, a 3-h application of 160 mg/g MAL showed the highest selectivity for tumour, and this procedure is licensed in the form of two treatments 1 week apart for BCC.<sup>15</sup> It is also licensed as a double treatment for SCC *in situ*, but in AK one treatment is recommended, with non-responders receiving a second treatment at 3 months. Nanoemulsion ALA is also applied for 3 h when using the conventional PDT protocol, with a repeat treatment at 1 week when treating BCC, but waiting to 3 months and assessing need for repeat therapy when treating AK.<sup>12</sup>

The 20% ALA formulation used with the Blu-U™ system (blue fluorescent lamps) is licensed for a drug light interval of 18–24 h but is widely used with application times of around 1 h for AK.<sup>16</sup> A shorter incubation time of 1 h with MAL for AK is also an option given that in a comparison of 1 h vs. 3 h, overall lesion response rates (after 1 or 2 PDT treatments) were 76% vs. 85%, respectively.<sup>17</sup>

Additional topically applied photosensitizers including indocyanine green, indole-3-acetic acid,<sup>18</sup> hypericin,<sup>19,20</sup> silicon phthalocyanine PDT<sup>21</sup> and 3,7-bis (*N,N*-dibutylamino) phenothiazin-5-ium bromide<sup>22</sup> have been assessed in specific indications but are not licensed, to date.

### Light sources and dosimetry

**Light sources for conventional PDT** A range of light sources can be used for topical PDT including filtered xenon arc and metal halide lamps, fluorescent lamps and light-emitting diodes (LED) and even lasers although coherent light is not required. Large fields can be treated using narrowband LED devices, e.g. the Aktilete 128 (Galderma), BF-Rhodo LED (Biofrontera) and Omnilux PDT (Phototherapeutics, London, UK) each with an output that matches the 630/635 nm activation peak of PpIX whilst excluding the extraneous wavelengths present in broadband sources, permitting shorter illumination times. Filtered intense pulsed lights (IPLs) have been successfully used in PDT

**Table 1** Treatment protocols for licensed indications

Indication	Preparation/drug application	Illumination recommendations	Protocol	Reference
16.0% MAL (Metvix® Lausanne, CH)	Conventional PDT: Thin, non-hyperkeratotic AK (face/scalp), SCC <i>in situ</i> , sBCC, nBCC Remove scales/crusts, roughen surface (remove intact epidermis over 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 <sup>2</sup> (red light with narrower spectrum, giving the same activation, can be used: ~630 nm, light dose of 37 J/cm <sup>2</sup> )	AK – one treatment, assess 3 months, SCC <i>in situ</i> and BCC – two sessions 7 days apart, reassess after 3 months. Remaining lesions may be retreated	Full details @ <a href="https://www.medicines.org.uk/emc/product/6777/smpc">https://www.medicines.org.uk/emc/product/6777/smpc</a> (accessed 5/2/19)
16.0% MAL (Metvix® Lausanne, CH)	Daylight PDT: mild to moderate AK <b>Apply sunscreen, once dried, scales and crusts should be removed and the skin surface roughened before applying a thin layer of Metvix to treatment areas. No occlusion</b>	Patient to go outside within 30 min, dry day with temperature >10°C, for 2 h	Single treatment, evaluate at 3 months, repeat if required	Full details @ <a href="https://www.medicines.org.uk/emc/product/6777/smpc">https://www.medicines.org.uk/emc/product/6777/smpc</a> (accessed 5/2/19)
8 mg 5-ALA (2 mg/cm <sup>2</sup> ) medicated plaster (Alacare®, Photonamic, Pinneberg, Germany)	Mild AK (<1.8 cm in diameter) face/bald scalp Apply medicinal plaster up to a maximum of 6 patches on 6 different lesions. Incubate for 4 h	After 4 h, remove and expose to red light (spectrum of 630 ± 3 nm, total light dose of 37 J/cm <sup>2</sup> )	Single use treatment, reassess after 3 months, retreat remaining lesions with alternative therapies	Full details @ <a href="https://www.medicines.org.uk/emc/product/8958/smpc">https://www.medicines.org.uk/emc/product/8958/smpc</a> (accessed 5/2/19)
78 mg/g 5-ALA gel (Ameluz®, Biofrontera, Leverkusen, Germany)	Conventional PDT: Mild to moderate AK face/scalp, field cancerization, superficial and/or nodular BCC Remove scales/crusts, gently roughen surface, degrease skin. Apply a layer of cream approx 1 mm thick and surrounding 5 mm of skin or <b>entire cancerized fields of about 20 cm<sup>2</sup></b> . Cover with occlusive dressing for 3 h	After 3 h, remove dressing, wipe clean, then illuminate using red light either with a narrow spectrum (~630 nm, light dose 37 J/cm <sup>2</sup> ) or a broad spectrum (570–670 nm, 75–200 J/cm <sup>2</sup> )	One treatment, reassess after 3 months, remaining lesions may be retreated	Full details @ <a href="https://www.medicines.org.uk/emc/product/3158/smpc">https://www.medicines.org.uk/emc/product/3158/smpc</a> (accessed 5/4/19)
78 mg/g 5-ALA gel (Ameluz®, Biofrontera)	Daylight PDT: Mild to moderate AK face/scalp, field cancerization, <b>Apply sunscreen, once dried, wipe with an ethanol or isopropanol-soaked cotton pad then remove scales and crusts, roughen skin surface before applying a thin layer of Ameluz to treatment areas. No occlusion</b>	Patient to go outside within 30 min, dry day with temperature >10°C, for 2 h	One treatment, reassess after 3 months, remaining lesions may be retreated	Full details @ <a href="https://www.medicines.org.uk/emc/product/3158/smpc">https://www.medicines.org.uk/emc/product/3158/smpc</a> (accessed 5/2/19)
20% ALA solution (Levulan Kerastick™, DUSA, Wilmington, MA, USA)	Minimal/moderate 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 <sup>2</sup> light dose BLU-J (1000 s), positioning lamp as per manufacturer's instructions (shorter application times are often used in practise)	One application and one dose of illumination per treatment site per 8-week treatment session	Full details @ <a href="http://www.dusapharma.com/kerastick.html">http://www.dusapharma.com/kerastick.html</a> (accessed 5/2/19)

for AK, acne and photorejuvenation although they emit different spectra, resulting in a need to derive specific protocols to achieve identical radiant exposures.<sup>23</sup> Narrow spectrum light sources are associated with higher response rates, with complete patient clearance rates of 85% and 68% for nanoemulsion ALA-PDT or MAL-PDT, respectively, compared with 72% and 61% when broad spectrum devices were used.<sup>12,24</sup>

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 use the 630 nm absorption peak in the red region, in order to improve tissue penetration, although a blue fluorescent lamp (peak emission 417 nm) is recommended in Levulan PDT. Light dose specifications are included in the product summaries of the topical photosensitizers approved for skin cancer indications, whilst dosimetry for emerging inflammatory/infective dermatoses discussed in Part 2 is not yet standardized. Consideration of high and low dose regimens for PDT in acne has been reviewed although an optimal protocol has not been established.<sup>7,25</sup>

**Fractionated illumination** Discontinuous illumination (fractionation) may improve the efficacy of PDT by permitting tissue re-oxygenation during 'dark' periods. Studies support superiority of fractionation to conventional illumination in ALA-PDT for AK (94% vs. 85% at 1 year) and sBCC (88% vs. 75% at 5 years), but not in SCC *in situ* (88% vs. 80% at 1 year).<sup>26–28</sup> Overall clearance of 95% after 2-year follow-up has been reported in a large series of 552 lesions (AK, SCC *in situ*, sBCC, nBCC) following ALA-PDT using two light fractions of 20 and 80 J/cm<sup>2</sup> at 4 and 6 h separated by a 2-h dark interval.<sup>29</sup> An alternative ALA-PDT fractionation protocol of two doses of 75 J/cm<sup>2</sup> at 4 and 5 h was associated with an initial 94% clearance rate for nBCC, but with a cumulative failure rate of 30% by 3 years.<sup>30</sup> No significant difference in efficacy was observed when standard red light MAL-PDT was compared with fractionated ALA-PDT in a study of 162 patients with superficial BCC.<sup>31</sup> No efficacy improvement has been reported using light fractionation in MAL-PDT, considered to be due to differences in localization between the agents.

**Daylight, ambulatory LED and fabric-based laser diode illumination** Daylight is increasingly used as the light source for PDT in treating AK, with application of either nanoemulsion ALA or MAL for 0.5 h, followed by exposure to daylight for 2 h, with no inferiority of efficacy to red light PDT, but with the benefit of reduced pain.<sup>32–34</sup> As well as its potential for AK and field cancerization, daylight PDT has been assessed for treating BCC.<sup>35</sup>

There is also an option for patients to wear a portable LED device, permitting ambulatory PDT to reduce the need for hospital attendance, with an overall 84% lesion clearance reported

for sBCC and SCC *in situ*, 1 year following two treatments, 1 week apart, with minimal pain with another research group demonstrating 90% clearance rate at 12 months in a study of 143 sBCC.<sup>36,37</sup>

A novel light-emitting, fabric-based laser diode device has recently been shown to be as effective as conventional PDT in clearing AK but with minimal pain, with MAL applied under a transparent occlusive dressing for 30 min then fabric device is applied and switched on after 30 min, remaining on for 150 min.<sup>38</sup>

### Lesion preparation

Protocols for topical PDT in Europe conventionally recommend some form of lesion preparation to enhance photosensitizing agent absorption and light penetration in MAL-PDT and nanoemulsion ALA-PDT. Studies using a novel ALA plaster for mild and moderate thickness AK do not require prior preparation with results consistent with standard protocols.<sup>13,39</sup> 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<sup>14,17</sup> whilst others have not noted increased drug uptake following lesion preparation of SCC *in situ* and BCC.<sup>40</sup> However, gentle removal of overlying crust and scale is commonly performed for moderate thickness/hyperkeratotic AK and for SCC *in situ* and superficial BCC. Lesion 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 practitioners perform a more formal lesion debulking days/weeks prior to PDT, with 92% of BCC clearing following a single session of ALA-PDT in one study.<sup>41</sup> The effect of pre-PDT deep curettage in another study of thick ( $\geq 2$  mm) BCC reduced mean tumour thickness from 2.3 mm (range 2.0–4.0) by 50%, with 3-month tumour response of 93%.<sup>42</sup> In a comparison study of PDT (ALA and MAL) with or without debulking immediately pre-photosensitizer application, residual nBCC was more often observed in lesions that were not debulked.<sup>10</sup> Under standardized conditions in a randomized clinical trial, PpIX accumulation was most enhanced after ablative fractional laser pretreatment, followed by microdermabrasion, micro-needling and curettage.<sup>43</sup>

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 the opportunity for deeper photosensitizer penetration before photoactivation. PDT with occlusion is routine in conventional MAL and nanoemulsion ALA-PDT, but is not performed when using Levulan PDT and no occlusion is required for daylight PDT.<sup>32–35</sup>

## Treatment protocols

### Conventional topical PDT

Recommended protocols for ALA-PDT and MAL-PDT using currently licensed photosensitizing agents for NMSC indications are summarized in Table 1. Conventional PDT involves application of a topically applied photosensitizing agent, occluded for 3–4 h depending on product, then illuminated typically by a narrowband red LED light source. Protocols employed in emerging indications are discussed with each indication.

### Daylight PDT (DL MAL-PDT, DL ALA-PDT)

Daylight PDT is performed with initial widespread application of an organic sunscreen followed approximately 15 min later by lesion preparation, then nanoemulsion ALA or MAL to treatment area, without occlusion (details Table 1).<sup>44</sup> Within 30 min of application, patients are exposed to daylight for 2.0 h with licensed approvals for AK and field cancerization.<sup>45</sup> Alternative methods of delivering light equivalent to daylight, but avoiding the limitations of climate considerations, are emerging, including simple use of a glasshouse and attempting to simulate daylight indoors.<sup>46</sup> The potential to deliver daylight MAL-PDT at home has demonstrated high levels of patient satisfaction, effectiveness and tolerability.<sup>47</sup>

### Ambulatory, textile, pulse and temperature-modulated PDT

The protocol for ambulatory PDT, using an inorganic LED device, involves lesion preparation (maximum size 1.8 mm) and cream application before the light-emitting ‘plaster’ is applied. The device automatically switches on after the incubation period, to deliver a total dose of 75 J/cm at 7 mW/cm, then off at end of procedure permitting treatment outwith the clinic.<sup>36,37</sup>

Studies are ongoing to refine ‘Textile PDT’ where red 635 nm light is delivered through fabric from laser diodes, to slowly expose the skin to the same light dose as for conventional PDT.<sup>38</sup> As light intensity is reduced and incubation short, treatment is almost pain-free. The fabric allows for uniform light distribution even on curved surfaces, with potential to treat much larger areas.

In a novel protocol ‘pulse-PDT’, MAL is applied for 30 min with red light illumination after 3 h, with equivalent efficacy to conventional MAL-PDT in treating AK when compared in a randomized clinical trial.<sup>48</sup> Treatment-induced erythema was reduced, with further reduction if a superpotent topical corticosteroid is applied just before and after PDT. Another centre has proposed ‘temperature-modulated PDT’ where sustained clearance of 90% of 724 AK at 1 year was achieved by warming the skin during 1 h of Levulan ALA incubation.<sup>49</sup>

### Fluorescence diagnosis

The detection of skin surface fluorescence, visible following application of ALA and MAL, can be utilized as a non-invasive

method to assist in lesion definition as well as in identifying persistent/recurrent disease that may not be clinically obvious.<sup>50</sup> Compared with relatively subjective assessment of fluorescence using the Wood’s lamp, a CCD camera system can provide semi-quantitative measurements of PpIX within dermatological lesions. The value of PpIX imaging to outline tumours has shown contradictory results in a review of published studies.<sup>51</sup> Even when utilized to reduce stages in Mohs surgery, the technique did not permit time saving overall.<sup>52</sup>

Measurement of fluorescence during MAL-PDT has shown extent of photobleaching, but not total initial PpIX fluorescence, as predictive of lesion clearance.<sup>53</sup> In another study, fluorescence diagnosis in keratinocyte intraepidermal neoplasias was unable to discriminate between lesions or proliferative activity, although hyperkeratosis was an important determinant of macroscopic fluorescence intensity.<sup>54</sup> Intensity of pain has been associated with fluorescence intensity and can help anticipate patients more likely to require active pain management.<sup>55</sup> In practice, in addition to helping predict likelihood of pain, PDT practitioners find observing strong fluorescence is helpful in supporting clinical suspicion of recurrence whilst absence can also be supportive of clinical indication of clearance of disease after treatment.

## Current indications

### Actinic keratosis (strength of recommendation A, quality of evidence 1) (approved indication)

**Conventional PDT for AK** Conventional PDT with 5-ALA, nanoemulsion 5-ALA and MAL has been widely studied for thin and moderate thickness non-hyperkeratotic AKs of the face and scalp with typical lesion clearance rates of 81–92% 3 months after treatment.<sup>12,13,24,56–58</sup> Conventional nanoemulsion ALA-PDT was superior to MAL in clearing thin and moderate thickness AK from face/scalp, with clearance of 90% vs. 83% of lesions (respective complete clearance rates of 78% vs. 64%) 12 weeks after one or two PDT treatments.<sup>12</sup> Similar lesion recurrence rates were observed following nanoemulsion ALA-PDT and MAL-PDT of 22% and 25%, respectively, at 12 months, with subset analysis showing improved response with lesions treated using the narrow wavelength LED lamps.<sup>59</sup> A randomized intra-individual study of 50 patients compared nanoemulsion ALA with MAL, demonstrating similar lesion clearance rate after a single treatment (ALA: 90%, MAL: 88%) but with more intense skin reactions observed with ALA, presumed due to less selectivity, although this was associated with higher accumulation of PpIX.<sup>60</sup> One year of lesion clearance rates of 78% and 63–79% have been reported following Levulan ALA-PDT (up to two treatments) and patch ALA-PDT (single treatment), respectively.<sup>39,61</sup> A randomized multicentre study of conventional nanoemulsion ALA-PDT achieved a patient



clearance rate of 91% (vs. 22% placebo) with additional benefits to skin quality in field-directed treatment of AK.<sup>62</sup>

**Comparison of conventional PDT with other therapies for AK** Compared with cryotherapy, MAL-PDT achieved an initially superior cure rate than cryotherapy (87% vs. 76%), but with equivalent outcome after retreatment of non-responders (89% vs. 86%) in a randomized intra-individual study of 1501 face/scalp AK.<sup>58</sup> ALA-PDT using the self-adhesive patch cleared 82–89% of mild or moderate AK in patients with 3–8 face/scalp lesions, superior to the 77% clearance rate in a comparator group receiving cryotherapy.<sup>13</sup> MAL-PDT is more effective than diclofenac and hyaluronic acid cream as well as to trichloroacetic acid, with non-formulary ALA-PDT more effective than CO<sub>2</sub> laser ablation, in separate comparison studies.<sup>63–65</sup>

Two systematic reviews looked at the use of conventional PDT against other therapies. A Cochrane Library systematic review searched databases up to March 2011, identifying 83 RCTs covering 18 AK therapies, including PDT.<sup>66</sup> Whilst the primary outcome ‘participant complete clearance’ significantly favoured four field-directed topical treatments compared to vehicle or placebo, it favoured the treatment of individual AK lesions with PDT compared to placebo-PDT with ALA using blue light, ALA using red light, and MAL with red light. ALA-PDT was also significantly favoured compared to cryotherapy. Based on investigator and participant evaluation, imiquimod and PDT resulted in better cosmetic outcomes than cryotherapy and 5-fluorouracil. A further systematic review performed in 2013 undertook to compare the evidence of the effectiveness of PDT compared with other therapies, restricted to RCTs with at least 10 participants.<sup>67</sup> Thirteen studies were included in the final synthesis, of which 4 were eligible for final meta-analysis. The only comparator for which meta-analysis was performed was cryotherapy. PDT was concluded to offer a 14% better chance of complete lesion clearance at 3 months after treatment than cryotherapy for thin AKs on the face and scalp.

**Combination of conventional PDT with other therapy for AK** There is emerging use of combination therapies in AK, either combining lesional with field therapy or two field therapies. A recent meta-analysis investigated whether conventional PDT combined with other field therapies is superior to PDT alone.<sup>68</sup> From 1800 references, 10 RCTs with a total sample of  $n = 277$  were included. Four studies explored the combination of PDT with imiquimod, three with 5-fluorouracil and one each with ingenol mebutate (IM) gel, tazarotene gel and calcipotriol ointment, respectively. Overall, patients treated with a combination showed significantly higher clearance rates compared with monotherapy. Considering the specific therapies, in a subset analysis, topical imiquimod combined with PDT, either prior to or following PDT, showed higher participant complete clearance

rates than monotherapy. Pretreatment with topical 5-fluorouracil cream, applied twice daily for 6–7 days prior to PDT (both ALA and MAL), led to a mean improvement in lesion clearance of 11–30% compared with PDT alone. Pretreatment of acral AK lesions with 0.1% tazarotene gel may also enhance the effect of PDT but this study only had 10 participants.<sup>69</sup> Combination ALA-PDT with ingenol did not achieve a significant differential response rate, but the response rate of 92% reduction in AK with ingenol alone is unusually high compared with routine practice.<sup>70</sup>

A randomized split-scalp study compared calcipotriol once day for 15 days prior to conventional MAL-PDT vs. conventional PDT. Clinical and histological improvement was superior on the calcipotriol-assisted side (overall AK clearance rates were 92.1% and 82.0%, respectively) with greatest improvement for grade II AKs (90% vs. 63%) although pain and also local side-effects were greater with the combined protocol.<sup>71</sup> A prospective randomized clinical trial using ablative fractional laser-assisted MAL-PDT after twice daily topical 0.005% calcipotriol pretreatment for 2 weeks showed a higher rate of complete response of facial AK with the combined treatment (89% vs. 80%) and lower recurrence rate at 12 months (5% vs. 10%).<sup>72</sup>

A systematic review and metaanalysis of laser-assisted PDT for AK identified seven randomized controlled trials with four included in the analysis.<sup>73</sup> Laser-assisted PDT showed significantly higher clearance rates than PDT monotherapy with no difference in pain intensity between laser-assisted PDT and PDT or laser monotherapy. Such an approach potentially complicates the ease of delivery of PDT and increases healthcare costs and may be best utilized for difficult to treat acral and/or hyperkeratotic AK and AK in the immunosuppressed.

**Daylight PDT for AK** DL MAL-PDT is as effective, but less painful, than conventional PDT with a randomized intra-individual trial of patients with multiple AK on face/scalp demonstrating a reduction, after a single treatment, of 79% on the daylight side compared with 71% when standard LED illumination was used.<sup>74</sup> Subsequent multicentre studies have demonstrated that daylight exposure of 1.5 h is as effective as 2.5 h, but that lesion response is highest for thin lesions (76%) compared with clearance rates of 61% and 49% for moderate and thick AK, respectively.<sup>75,76</sup> Reduced efficacy of thicker lesions was demonstrated in a trial with 3 months of clearance rates for types I, II, and III AK of 76%, 61% and 49%, respectively, after a single treatment of DL-PDT, with considerable variation in response between centres.<sup>76</sup> A study assessing the impact of latitude on its delivery identified that DL MAL-PDT can be performed throughout the summer and until mid-September in Reykjavik and Oslo, late October in Copenhagen and Regensburg, mid-November in Turin, and all year in Israel.<sup>77</sup> During these months, it should be possible to achieve active PpIX-weighted daylight dose as above 8 J/cm<sup>2</sup>,

and a maximum daytime temperature of 10°C, to permit effective treatment.

Two pivotal intra-individual multicentre comparative studies in Australia and Europe both observed that DL MAL-PDT was non-inferior to conventional PDT with the Australian study reporting lesion clearance rates of the mild AK treated of 89% and 93%, respectively, 12 weeks after one treatment session.<sup>32,33</sup> The European study observed equivalent responses of 70% and 74%, both values lower as this study included patients with mild and moderate thickness lesions. Daylight PDT was virtually pain free in comparison with conventional PDT and was as effective whether performed in sun or cloudy conditions. Both high efficacy and patient satisfaction were demonstrated in a further multicentre study conducted over six European countries, in 325 patients receiving a single treatment of DL MAL-PDT for face and/or scalp AK, demonstrated efficacy at 3 months was at least much improved in 83.5% of patients, with 45.9% of patients requiring no retreatment.<sup>78</sup>

DL ALA-PDT using nanoemulsion ALA has at least as effective as DL MAL-PDT in treating mild and moderate AK. In a randomized split-face trial, 13 patients with 177 grade I-III AK, DL ALA-PDT cleared 85% of AK compared with 74% treated by MAL.<sup>34</sup> The per-patient half-face analysis showed ALA to have a significantly higher clearance rate for grade I AKs than did MAL, but for thicker grades, clearance was equal. A recent multicentre intra-individual comparison trial has compared DL ALA-PDT with DL MAL-PDT in 52 patients with 3–9 mild to moderate thickness AK on the face/scalp.<sup>79</sup> Equivalent efficacy was demonstrated at 3 months, with lesion clearance rates of 79.8% with ALA and 76.5% with MAL, although recurrences at 1 year were higher with MAL (31.6% vs. 19.9%). In a non-sponsored randomized comparison trial, DL ALA-PDT was more effective than DL MAL-PDT in the per-patient half-face analysis of clearance (79.7% vs. 73.5%).<sup>80</sup> In an evaluation of patient self-application of DL MAL-PDT, there was high patient satisfaction and at 3 months, with 62% of treated AK were clear.<sup>47</sup>

**Comparison of DL-PDT with other therapies** There is limited direct comparison evidence of DL-PDT with standard therapies. DL-PDT has been compared with IM in the treatment of 27 patients with 323 grade I and II AK with identical response rate.<sup>81</sup>

**Combination therapy using DL-PDT** A case series of 11 subjects with grade I-III AKs evaluated with a split-face design the effect of once-daily calcipotriol ointment for 15 days prior to DL MAL-PDT compared with PDT alone. After 3 months, the complete response rate was 85% and 70% although the combination was associated with more erythema and desquamation.<sup>82</sup> A randomized controlled trial compared DL MAL-PDT followed by diclofenac/hyaluronic acid gel 30 days before or after, compared with PDT alone; after 12 months, no significant difference in

resolution of the AK was observed (91.2% vs. 90%).<sup>83</sup> Pretreatment with ablative fractional laser, compared with microdermabrasion, was more effective (81% vs. 60% AK clearance) in patients with extensive field cancerization using DL MAL-PDT in a recent randomized trial.<sup>84</sup>

**PDT for acral AK** Photodynamic therapy is less effective for AK on acral sites, probably in part due to a higher proportion of thicker lesions on these sites. A study comparing conventional MAL-PDT with cryotherapy for AK on the extremities demonstrated inferior efficacy with PDT, with clearance of 78% of lesions at 6 months compared with 88% for cryotherapy.<sup>85</sup> However, in a right/left comparison study with imiquimod, conventional ALA-PDT cleared significantly more moderate thickness AK lesions (58% vs. 37%), and equivalent numbers of thin AK on the hands/forearms (72% lesions).<sup>86</sup> A further randomized placebo-controlled study of MAL-PDT using an IPL to treat AK on the dorsal hands achieved complete remission of 55% compared with 3% with light alone.<sup>87</sup> Similar to conventional PDT, 7 days pretreatment with 5-fluorouracil cream has enhanced DL MAL-PDT in a study treating AK on dorsum of hands, with superior clearance rates after single PDT session of 62.7% vs. 51.8% compared with PDT alone.<sup>88</sup>

**PDT for actinic cheilitis** A series of 40 patients saw complete clinical response at 3 months in 26 patients with actinic cheilitis following conventional ALA-PDT although with histological evidence of recurrence in nine patients over 18 months of follow-up.<sup>89</sup> Conventional MAL-PDT clinically cleared 47% of 15 patients although histological clearance was evident in only 4.<sup>90</sup> In a retrospective analysis of real-life practice, PDT cleared 27 of 43 (63%) patients with complete response maintained at  $4.2 \pm 5.9$  months.<sup>91</sup> A recent systematic review of PDT in actinic cheilitis reviewed 15 eligible studies with a complete response of 62% at final follow-up ranging from 3 to 30 months, although histological cure, where assessed, was lower, at 47% overall at final follow-up (1.5–30 months).<sup>92</sup>

To achieve improved response rate, cotton rolls and lip retractors can be used, as well as considering repeat treatments and/or combining with other therapies. Sequential MAL-PDT then imiquimod cream achieved clinical clearance in 80% (histological 73%) in a study of 30 patients.<sup>93</sup> Ablative fractional laser pretreatment also has significantly improved response to use of PDT in actinic cheilitis, clearing 92% lesions at 3 months (compared with 59% by MAL-PDT alone), with an 8% recurrent rate (compared with 50% with MAL-PDT alone) at 12 months.<sup>94</sup>

Two recent publications detail DL MAL-PDT for actinic cheilitis which achieved sustained response in 5/10 patients over 6–12 months of follow-up in a study of two treatments 7–14 days apart, whilst a 91% cure rate in 10/11 patients was achieved using repeated treatments – mean 2.8.<sup>95,96</sup>

Therapy guidelines identify PDT as effective both as a lesion and field-directed treatment and suggest PDT has a role where AKs are multiple/clustering, as a suitable choice for patients wishing to manage background actinic changes, and as part of maintenance treatment for low-grade AKs in sun damaged skin.<sup>97,98</sup> PDT remains a predominantly hospital-based therapy in most countries whilst many patients with AK are treated by primary care physicians. However, high quality of cosmesis consistently observed in PDT studies for NMSC indications including AK, combined with increasing emphasis on patient choice over therapy, may see increased demand for topical PDT. A recent systematic review of AK clinical guidelines to construct a treatment algorithm positioned DL-PDT a valuable option for patients with multiple AKs in small or large fields.<sup>99</sup>

### **Squamous cell carcinoma *in situ* (Bowen's disease)/invasive SCC**

#### **Squamous cell carcinoma *in situ* (strength of recommendation A, quality of evidence 1) (approved indication)**

Lesion clearance rates of 88–100% are reported for SCC *in situ* 3 months after one or two cycles of conventional MAL-PDT, with 68–89% of treated lesions remaining clear over follow-up periods of 17–50 months.<sup>100–104</sup> Conventional MAL-PDT is approved in many countries for Bowen's disease, but no formulation of ALA-PDT is licensed.

In a Cochrane review of treatments for Bowen's disease, PDT appeared to be an effective treatment and offer the benefit of minimal scarring compared with cryotherapy or 5-fluorouracil.<sup>105</sup> There are limited data to demonstrate superiority of PDT to standard therapy, with conventional MAL-PDT compared with cryotherapy or topical 5-fluorouracil in a large European study with 3 month lesion response rates similar with all regimens (93% for MAL-PDT, 86% for cryotherapy, 83% for 5-fluorouracil).<sup>100</sup> Although PDT had a superior 1-year lesion clearance rates; all three therapies were similar after 2 years with 68% clear following PDT, 60% after cryotherapy and 59% after 5-fluorouracil.<sup>101</sup> A similar 3-month efficacy rate of 88% was observed in an open study of MAL-PDT for 41 SCC *in situ* with sustained clearance at 24 months of 71%.<sup>102</sup> Further open studies assessing durability of response to MAL-PDT observed 76% and 89% sustained clearance after follow-up periods of 17 and 50 months, respectively.<sup>103,104</sup> Non-formulary ALA-PDT has been compared with cryotherapy and with 5-fluorouracil in small studies where PDT proved superior in efficacy and adverse events in comparison with 5-fluorouracil, as well as being less painful compared with cryotherapy.<sup>106,107</sup>

Lesion size impacts on clearance rate with 82% of lesions up to 14 mm clear at 12 months reducing with increasing size to only 55% of lesions 30 mm or larger.<sup>100</sup> Larger plaques over 3 cm responded to a cycle of MAL-PDT, two treatments 7 days

apart, clearing 90% of 23 lesions and observing recurrence in only 3 up to 12 months reducing clearance to 83%, with another study of identical design initially clearing 90% of 37 lesions, noting four recurrences after 12 months reducing clearance rate to 78%.<sup>108,109</sup>

Emerging literature on combination PDT in comparison with PDT alone observes that ablative fractional laser-assisted MAL-PDT was significantly more effective than PDT alone in two studies, clearing 94% of plaques compared with 73% at 1 year in one study, whilst in a 5 year follow-up study, ablative laser-assisted MAL-PDT achieved sustained clearance rates of 85% vs. 45% with PDT alone.<sup>110,111</sup> A similar superiority of response has been observed in a small comparison trial of microinvasive SCC where ablative fractional laser-primed MAL-PDT achieved 3 months of clearance rates of 84% vs. 52% with PDT alone, with reduced recurrence rates (12% compared with 64% at 2 years for PDT alone).<sup>112</sup> ALA-PDT combined with CO<sub>2</sub> laser achieved clearance at 6 months of 64% of lesions compared with 18% with laser alone in a trial of 22 lesions.<sup>113</sup>

The therapeutic effect of PDT may be enhanced by sequential use along with topical imiquimod, although clinical experience, to date, is limited.<sup>114,115</sup>

Severe atypia and higher age were associated with increased risk of treatment failure following PDT in a retrospective study re-examining histology and clinical features of patients treated with PDT over 5 years.<sup>116</sup> Failure to correctly perform PDT may also impact efficacy with a national prospective observational study of MAL-PDT in France noting incorrect delivery of treatment in 23% of patients.<sup>117</sup>

A comprehensive disease-specific guideline pointed to the value of PDT for all lesions in poor healing sites and for large lesions in good healing sites, supported by a recent review.<sup>118,119</sup> PDT is considered a fair choice for small lesions in good healing sites, multiple lesions, facial, digital, nail bed and penile lesions, in comparison with other therapeutic options. In a patient-reported outcome study, satisfaction with ALA-PDT for SCC *in situ* was high, with 90% of respondents indicating a very favourable impression of the treatment, although with burning sensation described in 21%.<sup>120</sup> A national audit of use of PDT in clinical practice in Scotland confirmed that 27% of all use was for patients with Bowen's, just behind use for sBCC (33%) and AK (35%).<sup>121</sup>

#### **Invasive squamous cell carcinoma SCC (strength of recommendation D, quality of evidence 11-iii)**

There remain limited data on the efficacy of topical PDT for primary cutaneous invasive SCC although MAL-PDT can achieve higher response rates in microinvasive disease – 3-month clearance rates of 80%, with 58% still clear at 24 months.<sup>102</sup> Although 45% of nodular invasive SCC did appear to initially clear, clearance rate dropped to 26% by 24 months. The degree of cellular atypia is a negative prognostic factor, suggesting poorly differentiated keratinocytes are less sensitive to PDT. A



subsequent retrospective real-life audit of PDT identified an additional 17 invasive SCC (with initial clearance in 58.8%) with two recurrences reducing sustained clearance to 47%.<sup>91</sup> There is concern that not only does SCC not respond adequately to PDT, but that tumour could become more histologically aggressive and resistant to PDT. A study observed genomic imbalances related to CCND1, EGFRs and particularly MAP3K1 genes appear to be involved in development of resistance of SCC to PDT.<sup>122</sup> MAL-PDT was successfully used to treat verrucous carcinoma where surgery was contraindicated, indicating a case-specific role.<sup>123</sup> However, in view of its metastatic potential and reduced efficacy, PDT is not recommended for invasive SCC.

## Basal cell carcinoma

**Basal cell carcinoma: superficial basal cell carcinoma (strength of recommendation A, quality of evidence 1)**

**(approved indication) nodular basal cell carcinoma (strength of recommendation A, quality of evidence 1)**

**(approved indication) efficacy of PDT for sBCC and nBCC**

Initial clearance rates after conventional MAL-PDT of 92–97% for primary sBCC are reported, with recurrence rates of 9% at 1 year although 22% of initially responding lesions recurred over 5 years of follow-up.<sup>124,125</sup> 91% of primary nBCC were clear at 3 months following MAL-PDT, with a sustained clearance of 76% after 5 years.<sup>15,126</sup>

Histologically confirmed response rates were observed in a further two randomized studies of MAL-PDT for nBCC, with overall clearance in 73%, most effective for facial lesions where 89% achieved complete histological response.<sup>127</sup> 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 although the authors describe no debulking of the tumour prior to PDT.<sup>128</sup>

Ambulatory PDT has also been used to treat small sBCC with overall response rate for lesions on 84% at 1 year in one study and 90% in a more recent study.<sup>36,37</sup> There is limited experience of DL MAL-PDT for sBCC, which cleared 90% of 30 lesions at 3 months, although six recurrences occurred during 12 months of follow-up.<sup>35</sup> Sequential topical imiquimod 5% cream followed by DL MAL-PDT vs. PDT alone in sBCC achieved improved response rate if patient had two or more BCC, although no difference was observed for patients with single lesions.<sup>129</sup>

Nanoemulsion ALA-PDT was compared with MAL in the treatment of non-aggressive BCC in a randomized, phase III trial with 281 patients randomized. Of the ALA-treated patients, 93.4% were complete responders compared with 91.8% in the MAL group, establishing non-inferiority, with recurrence rate <10% by 1 year.<sup>130</sup>

In a randomized comparison trial of single vs. fractionated ALA-PDT for sBCC, 5 years after treatment, fractionated PDT produced a superior response (88% vs. 75%, respectively).<sup>27</sup>

Fractionated ALA-PDT was equivalent to surgery in initially clearing lesions but with a 31% failure rate over a median of 5 years after PDT, compared with only 2% postsurgery when a 75J/75J protocol was used although 80% of lesions remained clear at 2 years using a 20J/80J fractionated dosing.<sup>30,131</sup> Success of treatment depended on tumour thickness, with probability of recurrence-free survival over 5 years 94% if tumour  $\leq 0.7$  mm, compared with 65% for thicker lesions.

A study sought to evaluate whether fractionated ALA-PDT is superior to conventional MAL-PDT for sBCC. After 12 months, six treatment failures followed ALA-PDT with 13 after MAL-PDT. The 12-month cumulative probability of remaining free from treatment failure was 92.3% for ALA-PDT and 83.4% for MAL-PDT, failing to reach significance.<sup>31</sup> In a comparison of ALA-PDT vs. simple excision surgery for sBCC and nBCC, response rates were similar at 95.83% after PDT vs. 95.65% after surgery, with similar 25-month follow-up recurrence rates of 4.16% vs. 4.34%.<sup>132</sup>

**Comparison with other therapies** Methyl aminolaevulinate-PDT was equivalent to surgery (92% vs. 99% initial clearance, 9% and 0% recurrences at 1 year) for sBCC but inferior to excision for nBCC when recurrence rates are compared (91% vs. 98% initial clearance, 14% and 4% recurrences at 5 years).<sup>125,126</sup> Cosmetic outcome is superior following PDT. Clearance rates were equivalent when MAL-PDT was compared with 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 following PDT.<sup>124</sup> In a randomized pilot study of PDT with minimal curettage pre-ALA application vs. conventional surgery, there was also no evidence of superiority of PDT to surgery.<sup>133</sup> A single-blind randomized non-inferiority comparison of MAL-PDT (two treatments 1 week apart) with imiquimod cream or topical 5-fluorouracil for sBCC achieved tumour-free rates at 12 months of 73%, 83%, and 80%, respectively, falling to 58%, 80% and 68% at 36 months, indicating that using these protocols, 5-fluorouracil was non-inferior and imiquimod superior to one cycle of MAL-PDT.<sup>134</sup>

**Prediction of PDT response in BCC** Responsiveness of BCC is influenced by lesion thickness, with reduced efficacy with increasing tumour thickness in a study using ALA-PDT.<sup>135</sup> Lesions in the H-zone also have reduced sustained clearance rates.<sup>136</sup> A 10-year clinical and histological follow-up of 60 BCCs treated by ALA-PDT, originally <3.5 mm thick, reported 75% of treated sites remained disease free at 120 months.<sup>137</sup>

There has been debate whether treatment failures of BCC could be due to PDT modifying histological subtype. However, a recent study reported aggressive treatment failure recurrences after non-invasive therapy for superficial BCC occur most often within the first 3 months post-treatment, probably indicating

under diagnosis of more aggressive components in the primary tumour rather than transformation.<sup>138</sup>

**Combination therapy with PDT for BCC** Results, to date, are mixed regarding the advantage of pretreatment with laser before PDT for BCC. Combined therapy using an UltraPulse CO<sub>2</sub> laser and MAL-PDT with repeat PDT 1 week later achieved a recurrence-free clearance rate of 97% after a mean follow-up of 32 months, in 177 BCC of different subtypes, similar to the 100% clearance rate at 18 months for 13 nodular BCC treated with this combination.<sup>139,140</sup> Fractional laser as pretreatment before ALA-PDT for nBCC increased response rate from 80% to 93%.<sup>141</sup> In a randomized trial, facial nodular BCC received Er:YAG AFL-PDT (one session) or conventional MAL-PDT (two sessions), with clearance at 3 months of 76% with AFL-PDT and 43% with MAL-PDT.<sup>142</sup> However, in a further comparison of combined laser with PDT, response rate was only slightly increased to 99% compared with 95% for MAL-PDT alone in a study of nBCC using a Er:YAG laser.<sup>143</sup> Long-term efficacy was similar after MAL-PDT and fractional laser-mediated PDT for high-risk facial BCC with clearance at 12 months of 63% compared to 56% for PDT alone.<sup>144</sup>

A pilot study of 34 patients supplemented Levulan ALA-PDT with topical imiquimod cream (twice weekly for 5 weeks after PDT) for recurrent BCC observed higher clearance rate of 75% with the combination compared with 60% by PDT alone.<sup>145</sup> Combining imiquimod with MAL-PDT for BCC may achieve improved response, but requires further study beyond current case series.<sup>146–148</sup>

Patients with naevoid basal cell carcinoma syndrome (NBCCS) can benefit from PDT with several series and cases reported. A large cohort of 33 patients were treated by topical or systemic PDT depending on whether lesions were less than/greater than 2 mm in thickness when assessed by ultrasound, with an overall local control rate at 12 months of 56.3%.<sup>149</sup> A short report observed that MAL-PDT for NBCCS improves patient satisfaction and reduces the need for surgical procedures.<sup>150</sup>

Conventional MAL-PDT or nanoemulsion ALA-PDT should be considered in patients with non-aggressive, low-risk BCC, i.e. superficial and nodular types, not exceeding 2-mm tumour thickness, where surgery is not suitable or contraindicated due to patient-related limitations (comorbidities, medications, logistic difficulties).<sup>6</sup> Less common histologic variants, morpheic, pigmented and micronodular types, as well as areas with higher risk of tumour survival and deep penetration (facial 'H'-zone), should not be treated with PDT. A systematic review and meta-analysis concluded that PDT is effective for low-risk BCC, with excellent cosmesis and safety. Imiquimod has higher efficacy than single-cycle PDT but more adverse effects, with surgery offering the highest efficacy.<sup>151</sup> This is in accordance with a further review and meta-analysis of sBCC treatment options, where pooled estimates from randomized and nonrandomized studies

showed similar tumour-free survival at 1 year for imiquimod and PDT, with highest success in studies with repeated treatments.<sup>152</sup> PDT is recommended as a good therapy for primary sBCC, fair for primary low-risk nBCC and the treatment of choice for large low-risk primary sBCC.<sup>153</sup>

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