

Update on topical photodynamic therapy for skin cancer

C.A. Morton¹, R.-M. Szeimies², L.R. Braathen³

¹ Department of Dermatology, Stirling Community Hospital
Stirling, FK8 2AU, UK

² Dept. of Dermatology & Allergology, Klinikum Vest GmbH, Knappschaftskrankenhaus Recklinghausen
Dorstener Strasse 151, D-45657 Recklinghausen, Germany

³ Dermatology
Bern

Topical photodynamic therapy has become an established therapy option for superficial non-melanoma skin cancers with a substantial evidence base. In this update the increased choice in photosensitizers and light sources are reviewed as well as novel protocols to move beyond lesional treatment and address field therapy. Daylight PDT is emerging as an alternative to conventional office/hospital-based PDT that offers the advantage of much reduced pain. Although most studies have assessed efficacy of PDT in immune-competent patients, there is accumulating evidence for topical PDT being considered an option to assist in reducing the skin cancer burden in organ transplant recipients. The fluorescence associated with photosensitizer application can help delineate lesions prior to full treatment illumination and offers a useful adjunct to treatment in patients where diagnostic uncertainty or poor lesion outline complicates clinical care. PDT may also offer significant benefit in delaying/preventing new cancer development and combined with its recognized photo-rejuvenating effects, is emerging as an effective therapy capable of clearing certain superficial skin cancers, potentially preventing new lesions as well as facilitating photo-rejuvenating effects in treated areas.

Ключевые слова: **5-aminolaevulinic acid, methyl aminolaevulinate, non-melanoma skin cancer, topical photodynamic therapy.**

Контактная информация: colin.morton@nhs.net. Вестник дерматологии и венерологии 2014; (6): 26—34.

Introduction

Photodynamic therapy (PDT) involves the activation of a photosensitizing drug by visible light to produce reactive oxygen species within target cells, resulting in their destruction. PDT is widely used for the treatment of actinic keratoses (AK), squamous cell carcinoma in-situ (Bowen's disease — SCC *in-situ*) as well as superficial and thin nodular basal cell carcinomas (BCC) around the world [1—3]. Patients with large and/or multiple lesions, especially in poor healing sites, are most suitable for PDT. As PDT is tissue sparing and associated with a high quality cosmetic outcome, it has a place in treating lesions on cosmetically important sites — e.g. face and to reduce the need for large scars/grafts for superficial skin cancers. PDT can be used both, as lesional or as area/field-therapy, and has the potential to delay/reduce the development of new AK and BCC, although direct evidence of prevention of invasive squamous cell carcinoma remains limited [4].

The concept of PDT is not new, but over the past 25 years extensive research has been performed to perfect the use of topically active drugs, thus avoiding generalized photosensitivity that followed earlier systemic administration. Several systemic drugs are used for PDT for internal cancers, but have a more limited role for cutaneous indications and are not discussed further in this review.

PDT has also been studied for its place in the treatment as well as potential to prevent, superficial skin cancers in immunosuppressed patients, although sustained clearance rates are lower than when used in immunocompetent individuals [5]. Additional reported uses of topical PDT include local patch/plaque cutaneous T-cell lymphoma and extra-mammary Paget's Disease. In addition, PDT can improve acne and several other inflammatory/infective skin conditions, and improves several aspects of photoageing [4]. Despite extensive experience beyond NMSC, there are currently no licensed ap-

provals for its wider use, and this review focuses on the reported cancer indications of PDT.

Treatment is generally well tolerated but discomfort or pain is commonly experienced and alterations in the way PDT is delivered, including the use of daylight or other less intense light sources, and shorter photosensitizer application times, can reduce discomfort, whilst efficacy appears to be maintained at least in the treatment of actinic keratoses.

Topical photosensitizers

Current topical PDT involves application of a pro-drug, a precursor to the actual photosensitizer, onto the surface of the lesion/treatment area. Excess application of aminolevulinic acid (ALA) or its methyl ester, Methyl aminolevulinate (MAL), is taken up by the target cells, driving the haem synthesis pathway and results in accumulation of photoactive porphyrins, principally photoporphyrin IX (PpIX) [2, 6, 7]. These porphyrins are activated by light to produce reactive oxygen species that cause destruction, accompanied by host inflammatory and immune responses. There is selective uptake of photosensitizer through altered epidermis overlying lesional skin. In addition, proliferating, relatively iron deficient tumor cells preferentially accumulate PpIX.

Four products licensed in certain parts of the world for topical PDT are:

1. Methyl aminolaevulinate (160mg/g) (MAL) Metvix®/Metvixia® (Galderma, Lausanne, Switzerland) is used along with red light to treat non-hyperkeratotic actinic keratoses (AK), squamous cell carcinoma in-situ (SCC in-situ/Bowen's disease), superficial and nodular basal cell carcinomas (sBCC, nBCC).

2. A nanoemulsion of ALA (Ameluz® (Biofrontera AG, Leverkusen, Germany)) is licensed for PDT in combination with red light for the treatment of mild and moderate AK.

3. A patch containing 5-ALA (Alacare® (Galderma-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.

4. A 20% formulation of 5-ALA, Levulan (DUSA Pharmaceuticals, 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, creating difficult in making direct comparison between studies.

Light sources and daylight

Coherent laser light is not necessary for PDT and a wide range of light sources are available, including filtered lamps (xenon arc, metal halide, tungsten/halogen), fluorescent lamps and light-emitting diodes (LED) [2, 3]. Most employ red light with emission including the 630-5nm absorption peak of PpIX, to maximize penetration of light into tissue when treating all superficial skin cancer indica-

tions. Less penetrating shorter wavelength light, i. e. blue & green, are also effective in AK, with a blue fluorescent light approved for the treatment of AK by ALA in the US and several other countries.

Large fields can be treated using narrowband LED devices e. g. the Aktilite 128 (Galderma, Paris, France), BF-Rhodo LED (Biofrontera, Leverkusen, Germany) 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 e. g. PhotoDyn 750/505 (Hydrosun, Germany) and Waldmann PDT 1200L (Waldmann, Germany), permitting shorter irradiation times. Filtered intense pulsed lights (IPLs) have been successfully used in PDT for AK although they emit different spectra because of different filter technologies, resulting in a need to derive specific protocols for each model of lamp [8].

Narrow spectrum LED 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, 10].

Daylight is increasingly used as the light source for topical PDT for actinic keratoses, following studies indicating equivalent efficacy of MAL-PDT whether using daylight or a LED light source [11]. Blue light accounts for a high proportion of the effective light. There is minimal accumulation of PpIX with daylight PDT promoting a virtually pain-free treatment. The nanoemulsion formulation of ALA has recently been compared with MAL-PDT and shown to be at least equivalent for all grades of AK [12].

PDT using a low irradiance inorganic light-emitting diode source with peak wavelength of 640 nm in a plaster that is applied over the lesion, along with a battery pack, permits ambulatory PDT and has been assessed for use in small superficial nonmelanoma skin cancers (NMSC) [13].

Although the ambulatory device is limited to lesional PDT, daylight and the large area LED sources are most appropriate for field PDT.

Fluorescence diagnosis

Following application of ALA and MAL, porphyrin accumulation permits red fluorescence to be demonstrated, permitting lesion definition as well as identification of persistent/recurrent disease that may not be clinically obvious [14]. Subjective assessment of fluorescence can be performed by using Wood's lamp systems (370–405 nm), although a CCD camera system has been developed that can provide semi-quantitative measurements of PpIX within dermatological lesions. Fluorescence diagnosis has not been shown to be substantially superior to simple clinical assessment of tumour margins [15]. PpIX fluorescence imaging to determine tumour boundaries during Mohs micrographic surgery has been assessed with inconsistent results regarding improvement in surgical efficacy [16].

Measurement of fluorescence during MAL-PDT has shown extent of photobleaching, but not total initial protoporphyrin IX fluorescence, to be predictive of lesion clearance [17]. Intensity of pain has been associated with fluorescence intensity and can aid PDT practitioners in recognizing those patients more likely to require active pain management [18].

Protocols for the delivery of PDT

Several protocols have been assessed, often specific to the photosensitizer and light source used. Approvals for their use varies between countries depending on licence, with protocols outlined below quoting product information current at performance of this review, rather than study protocols that often evolve during the research cycle of a product:

Conventional MAL-PDT [19]: Indicated for thin, non-hyperkeratotic AK (face/scalp), SCC in-situ, sBCC, nBCC. Remove scales/crusts, roughen surface (remove intact epidermis over nBCC). Apply a layer of cream approximately 1 mm thick via spatula to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 hours, then wipe clean with saline. After 3 hours, remove dressing, wipe clean with saline, then illuminate using red light of spectrum 570–670 nm, total dose 75 J/cm² (red light with narrower spectrum, giving the same activation, can be used: ~630nm, light dose of 37 J/cm²). AK — one treatment, assess 3 months, SCC in-situ and BCC — two sessions 7 days apart. Treatment sites should be reassessed after 3 months and remaining lesions retreated.

Conventional ALA-PDT using nano-emulsion ALA [20]: Indicated for mild to moderate AK 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 mm of skin. Cover with occlusive dressing for 3 hours. After 3 hours, remove dressing, wipe clean, then illuminate using red light either with a narrow spectrum (~630 nm, light dose 37 J/cm²) or a broader, continuous spectrum (570–670 nm, light dose 75–200 J/cm²). Reassess 3 months after one treatment and retreat if required.

Conventional ALA-PDT using medicated ALA plaster [21]: Indicated for thin AK (≤ 1.8 cm in diameter) face/bald scalp. Apply up to 6 plasters on different lesions, without need for lesion preparation. Incubate for 4 hours then remove plaster and expose to red light with a narrow spectrum device (spectrum of 630 \pm 3 nm, total light dose of 37 J/cm²). Single use treatment, reassess after 3 months, with current licence stating retreat remaining lesions with alternative therapies.

Conventional blue-light ALAPDT [22]: Indicated for thin/moderate AK on face/scalp. Lesions should be clean and dry. Following solution admixture, apply directly to lesions by dabbing gently with the wet applicator tip, and re-apply once dry. Treatment site not occluded, but protect from sun/bright light. After 14–18 hrs, 10 J/cm² light dose BLU-U (1,000 sec), positioning lamp as per manufacturer's instructions. One application and one illumination per treatment site per 8-week treatment session.

Daylight PDT [23]: Recently licensed for use in Australia for the treatment of thin or non-hyperkeratotic and non-pigmented AK on the face and scalp. If the weather is suitable to stay comfortably outdoors for 2 hours, apply a sunscreen (SPF 30 or higher) that does not include physical filters (eg. titanium dioxide, zinc oxide, iron oxide) 15 minutes prior to lesion preparation. The surface and surrounding area of the AK lesions should be prepared by removing scales and crusts and roughening the surface of the lesions. MAL cream is then applied but no occlusion is necessary. Daylight exposure should begin within 30 minutes and continue for 2 hours. During this time, patients should remain outside and carry out usual daily activities. On sunny days, should the patient feel uncomfortable in direct sunlight, shelter in the shade may be taken. Following the 2 hour exposure period, Metvix cream should be removed with saline water. Treated lesions should be evaluated after 3 months and, if necessary, a second treatment session should be repeated.

Ambulatory PDT: Uses an approved light source emitting light within the bandwidth specified by PDT protocols in many countries. Initial gentle scraping of a lesion, typi-

Table Advantages and disadvantages of topical PDT

Advantages	Disadvantages
Relatively selective treatment	Require staff, facilities to administer treatment
Non-invasive, tissue sparing	Requirement for most patients to attend hospital for PDT
Multiple lesions may be treated simultaneously	Interval between cream application and illumination can be inconvenient to patient
Supervised outpatient procedure	Pain during PDT — depending on site and field size
Repeated treatments possible	No tissue sample, thus no confirmation of completeness of response
Unlikely to complicate subsequent surgery, if required, as minimal scarring occurs	Daylight PDT dependent on weather; limited treatment season in northern latitudes
Good/excellent cosmesis — superior to certain standard therapies	

cally sBCC or SCC in-situ is followed by application of a thin layer of photosensitizing drug (ALA or MAL) to include a 5mm rim of surrounding normal skin and secured by a translucent dressing [13]. The light emitting 'plaster' is then applied the lesion and the patient can return home or to work. The device automatically switches on after the incubation period (3—4 hours depending on photosensitizing agent) to deliver a total dose of 75 J/cm² at 7mW/cm². Research is ongoing regarding other approaches to ambulatory PDT, including integration of optical fibres in a flexible textile structure coupled to a portable laser light source adjustable to the appropriate wavelengths [24].

Fractionated PDT: Fractionation involves splitting the dose of light, typically into two 'fractions' divided by a sufficient intervening 'dark' period to allow for the accumulation of more photosensitizer and re-oxygenation of tissue. This 'two-hit' approach, applying photosensitizing agent only once, but then illuminating the treatment field twice, has been widely researched and had shown benefit in certain NMSC using ALA, but not MAL. For best result, the initial dose should be relatively small compared with the second. The absence of any benefit when using MAL, the most widely licensed product in Europe, combined with the prolonging of treatment if a 2 hour dark intervals follows an initial treatment at 4 hours, has reduced the adoption of fractionated PDT which is currently not licensed as a PDT protocol [25].

Studies have so far shown superiority of fractionation compared with conventional illuminations in ALA-PDT for superficial BCC, but not in SCC in-situ [26, 27]. Overall clearance of 95% after 2 year follow-up has been reported in a large series of 552 lesions (AK, SCC in-situ, BCC) following ALA-PDT using two light fractions of 20 and 80 J/cm² at 4 and 6 hours separated by a 2 hour dark interval [28]. Another group has confirmed these high efficacy results for AK treated by ALA-PDT, with clearance at 12 months of 94% compared with 85% for lesions treated to standard protocol (2 treatments 7 days apart) [29]. An alternative ALA-PDT fractionation protocol of two doses of 75 J/cm² at 4 and 5 hours was associated with an initial 94% clearance rate for nBCC, but cumulative failure rate of 30% by 3 years [30].

Current indications for PDT

Actinic keratoses:

Evidence-based review guidelines quote clearance rates for AK on the face and scalp treated by topical PDT of 81—92% three months after treatment [1—3]. One year lesion clearance rates of 78% and 63—79% have been reported following ALA-PDT (up to 2 treatments) and patch ALA-PDT (single treatment) respectively [31, 32].

A randomized intra-individual study of 1501 face/scalp AK in 119 patients compared MAL-PDT with cryotherapy [33]. After the initial cycle of treatments, PDT resulted in a significantly higher cure rate than cryotherapy (87% vs. 76%), but with equivalent outcome after non-responders were retreated (89% vs. 86%).

ALA-PDT using a 20% formulation and blue light, studied to protocol application interval of 14—18 hours, cleared 75% or more of all lesions (4—7 face/scalp AK/patient) in 77% patients increasing to 89% after a second treatment [34].

ALA-PDT using the BF-200 nano-emulsion was superior to MAL in clearing thin and moderate thickness AK from face/scalp with clearance of 90% vs. 83% of lesions 12 weeks after one or two PDT treatments [9]. Another randomized study observed clearance of 81% of lesions following BF-200 ALA PDT compared with a 22% placebo response. Superior clearance rates were noted in this study in the subset of patients treated using a narrowband red LED source (96% and 99% respectively) compared with broadband light. After 12 month follow-up, similar recurrence rates were observed following BF 200 ALA-PDT and MAL-PDT with lesion recurrence rates of 22% and 25% respectively [35].

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 [36]. Twelve months after the single treatment, patch ALA-PDT remained superior in efficacy to cryotherapy [31].

MAL-PDT using daylight is as effective and associated with minimal discomfort, compared with conventional PDT, with a 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 [37]. Subsequent multicentre studies using daylight exposure of 1.5 hours is as effective as 2.5 hours, but response rates are typically lower for thicker lesions [38, 39]. A study assessing the impact of latitude on delivery of daylight PDT identified that daylight PDT can be performed throughout summer and until mid-September in the northern latitudes studies, in Reykjavik and Oslo [40].

Recently, a comparison split-face prospective study from Finland has been presented comparing daylight PDT using either nano-emulsion formulation of ALA with MAL in 13 patients with 177 AK. Nanoemulsion ALA cleared 85% of lesions, MAL cleared 74%, with superiority regarding thin AKs, but equivalent clearance rates for thicker grades [12].

Actinic cheilitis has also been successfully treated by ALA-PDT, with 26/40 patients showing clinical response at 3 months although with histological recurrence in 9 patients over 18 months follow-up [41]. MAL-PDT clinically cleared 47% of 15 patients in another case series although histological clearance was evident in only 4 of the 7 patients who appeared clinically clear [42]. A retrospective analysis of PDT across 20 Italian Dermatology departments, actinic cheilitis observed clearance of 27 of 43 (63%) patients [43]. Improved outcome might be achieved via combination therapy with sequential MAL-PDT then imiquimod 5% cream achieving clinical cure of 80% and histological cure of 73% in 30 patients [44].

European Dermatology Forum guidelines for actinic keratoses note the high efficacy of PDT for multiple AK on the face and scalp, with efficacy poorer for acral sites [45]. Guidelines from the UK recommend PDT as effective both as a lesion and field directed treatment for AK especially for multiple and/or confluent AK, at sites of poor healing, or where there has been a poor response to other topical therapies [46].

Topical PDT is a good option where field therapy to multiple AK is required, with the advantage that this can be delivered by a nurse/clinician and does not require prolonged application of irritant topical chemotherapy agents with the inevitable fall-off in compliance with use.

SCC-in situ (Bowen's disease)

Topical PDT has been widely studied for the treatment of SCC in-situ with evidence to indicate its particular advantage in treating patients with large and/or multiple lesions. In a comparison of MAL-PDT with clinician's choice of cryotherapy or topical 5-fluorouracil (5-FU) complete response rates 3 months after the last treatment were similar with all therapies (93% for MAL-PDT, 86% for cryotherapy, 83% for 5-FU) but PDT gave superior cosmetic results [47]. Response rates for the three therapies were also similar after 2 years with 68% of lesions cleared following PDT, 60% after cryotherapy and 59% after 5-FU [48]. Additional open studies report clearance rates of 71–89% after follow-up periods of 17–50 months [49–51].

MAL-PDT is effective in treating lesions over 3 cm in diameter, with 22/23 lesions showing complete clinical response 3 months after one treatment cycle of two sessions 7 days apart, with only 3 lesions recurring over a 1 year follow-up [52]. Similarly, ALA-PDT cleared 88% (35/40) of SCC in situ with a diameter greater than 2 cm, although four patches recurred within 1 year [53]. In 10 further patients with multiple (three or more) SCC in situ, 98% (44/45) of patches cleared, although four lesions recurred over 1 year.

Ambulatory PDT has potential for small plaques of SCC in-situ and superficial basal cell carcinomas with an 84% response rate at 1 year in a study using ambulatory PDT in NMSC lesions including 10 SCC in-situ [13].

Therapy guidelines recommend PDT as the treatment of choice for both large and small plaques on poor-healing sites, representing the majority of lesions, and a good choice for large lesions in good-healing sites [54].

Basal cell carcinoma

MAL is currently the only photosensitizing agent approved for the treatment of superficial and/or nodular BCC, Initial clinical clearance rates of 92–97% for primary superficial BCC with 9% recurrence rates at 1 year are encouraging although 22% of initially responding lesions recurred over 5 years [55, 56].

Primary nodular BCC can also respond to MAL-PDT with a clinical clearance of 91% at 3 months and a sus-

tained lesion clearance response rate of 76% after 5 years of follow-up [57, 58]. Poorer histological response rates with MAL-PDT for nodular BCC of 73% was reported in one study and 33% in another [59, 60].

Although PDT is usually delivered using red LED light sources for BCC, a pilot study used daylight with 90% of 30 lesions clearing 3 months after a single cycle of two treatments one week apart, although 6 recurrences during follow-up left a 12 month clearance rate of 74% [61]. ALA has also been widely used in treating BCC, with a weighted initial clearance rate of 87% noted for superficial BCC treated by ALA-PDT in a review of 12 studies, compared with 53% for nodular lesions [62]. Reduced efficacy with increasing tumour thickness and for lesions situated within the H-zone [63, 64].

MAL-PDT is equivalent to surgery for superficial BCC but inferior to excision for nodular BCC in pivotal studies each with 5 year follow-up, but cosmetic outcome is superior following PDT compared with surgery [57, 58]. MAL-PDT is equivalent in efficacy to cryotherapy with overall clearance after 5 years identical at 76% but with superior cosmesis following PDT [55]. In a comparison of MAL-PDT with imiquimod cream or topical 5-fluorouracil for superficial BCC tumour-free rates at 12 months of 73%, 83%, and 80% respectively, indicating that 5-fluorouracil is non-inferior and imiquimod superior to one cycle of MAL-PDT [65].

Patients with naevoid basal cell carcinoma syndrome (NBCCS) can benefit from PDT with several series and cases reported, although systemic PDT may be more efficacious where multiple thick lesions [66].

European guidelines for basal cell carcinomas recommend PDT as a first line treatment for superficial BCC alongside imiquimod, cryosurgery, curettage and laser, with surgery an option for small lesions. PDT is recommended as a second line treatment for nodular BCC, after surgery or curettage, alongside imiquimod and cryotherapy [67]. Use of PDT should take into account site to be treated, with preference to avoid high risk 'H' zones on face. PDT should not be used for high risk BCC (morphoeic, ill-defined, aggressive histology, recurrent (except sBCC) and nBCC > 1 cm in a high risk zone). 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 [68].

Invasive squamous cell carcinoma (SCC)

There is reduced efficacy of PDT for micro-invasive and nodular invasive SCC where 24 month clearance rates of 57% and 26% have been reported with the degree of cellular atypia is a negative prognostic factor [49]. In view of its metastatic potential and reduced efficacy rates, PDT currently cannot be recommended for invasive SCC.

Treatment and prevention of non-melanoma skin cancer in organ transplant recipients (OTR)

Review of the literature indicates the potential benefit of topical PDT to immunosuppressed patients including organ transplant recipients in treating certain NMSC lesions and achieving delay and possible prevention of a proportion of new lesions. However, efficacy appears less than when PDT is performed in immunocompetent patients, perhaps due to differences in immune response as well as the frequent observation of OTR recipients presenting with a greater disease burden, with a larger number of intra-epithelial lesions, including a higher proportion of lesions that may be less responsive due to hyperkeratosis.

A prospective study compared the efficacy of ALA-PDT for AK and SCC in-situ in OTR and immunocompetent with equivalent initial clearance rates of 88% and 94% respectively, but falling to 48% and 72% by 48 weeks [5]. Initial clearance rates are similar following MAL-PDT of 71% — 90%, with lowest response for acral lesions. [69, 70] MAL PDT was compared with topical 5-fluorouracil in a small inpatient comparative study: At 6 months, 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%) [71]. ALA-PDT cleared 30/32 facial tumours (21 BCC, 8 AK, 1 keratoacanthoma) in 5 OTR patients after 1-3 treatments although 2 invasive squamous cell carcinomas (SCC) did not respond [72].

The potential of PDT to delay skin cancer development is a particularly attractive option in OTR patients. A single treatment with MAL-PDT significantly delayed, by approximately 3 months, compared with control sites, development of new lesions in 27 renal OTR with AK and other skin lesions [73]. At 12 months, 62% of treated areas were free from new lesions compared to 35% in control areas. Five treatments of MAL-PDT over 15 months 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 suggesting additional treatments are required to maintain a protective effect [74].

No significant difference in the occurrence of SCC was observed in a study of ALA-PDT versus no treatment after 2 years follow up in 40 OTR.75 However, in another study of ALA-PDT, repeated at 4—8 week intervals for 2 years, a reduction in the incidence of SCC in 12 OTRs was observed compared with the number developing in the year prior to treatment, with a mean reduction at 12 and 24 months of 79% and 95% [76].

PDT for field cancerization

Skin field cancerization, the presence of multiple NMSC, AK and dysplastic keratinocytes in sun exposed areas, may be a good indication for topical PDT [77]. A recent consensus noted that PDT in field cancerization treatment in OTR could prevent new AKs and the transformation of AK to invasive SCC in a secondary prevention strategy, proposing

cyclic PDT with at least 2 initial treatments repeated several times over a year, possibly at 3 monthly intervals [78].

In addition to the studies in OTR reported above, the preventive potential of field PDT in the immunocompetent 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 [79]. PDT can decrease expression of p53, a marker of early skin cancer, supporting its preventive indication in carcinogenesis [80, 81].

This indication requires intensive study to confirm the observations from typically small studies, to clarify the extent to which PDT might truly prevent, rather than delay the development of de novo skin cancers and precursor lesions.

Cutaneous T-cell Lymphoma (CTCL)

Topical PDT has been used in localized CTCL, with selective uptake of photosensitizers into lymphocytes observed, although much of the evidence derives from case reports and case series. [4] 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. [82] MAL-PDT achieved complete remission in four of five patients with unilesional patch, plaque and nodular disease after a median of 6 treatments in one study [83], and clearance of 6/12 patients with plaque-type lesions after a mean of 5.7 treatments in another study [84]. In these two reports, no recurrences were seen after 6—24 months. In another series, 10 patients with unilesional patch- and plaque- stage CTCL were treated with 2—6 MAL-PDT treatments at one-week intervals. Both clinical and histological clearance was seen in five patients and a partial remission in two, with relapse only in one during 8—31 months follow-up [85]. In a further retrospective study of 12 patients with up to paucilesional MF, a 75% one-month response rate (6 complete responders, 3 partial) was observed following monthly MAL-PDT repeated over 6 months, with regression of lymphocytic infiltrate in 8/9 lesions biopsied [86].

Real-life use across several Italian centres suggests a possibly lower efficacy, with complete remission in only 5/19 patients with unilesional plaque stage or isolated CTCL lesions in body flexures with two relapsing during follow-up [43].

Other Skin Cancer Indications

PDT may offer an alternative for treating penile intraepithelial neoplasia, with one large series, using ALA- and MAL-PDT in 10 patients noted clearance in 7, but later recurrence in 4 [87].

On current evidence PDT probably has only a limited role as monotherapy in extra-mammary Paget's disease (EMPD). ALA-PDT initially cleared 8/16 EMPD lesions in 5 patients at 6 months, but with 3 recurring after a further 4 months [88]. Seven patients with recurrent EMPD of the vulva were treated using MAL-PDT and red light, with clearance in 4 [89]. PDT with the ALA applied via a bioad-

hesive patch cleared vulval EMPD after 4 treatments, with histological confirmation [90].

Adverse effects

Pain/burning sensation is commonly experienced during PDT, although varies widely in severity, usually developing within minutes of light exposure and likely reflects nerve stimulation and/or tissue damage by reactive oxygen species, aggravated by hyperthermia. Pain is more likely to be experienced if large fields are treated and is more common when treating AK than Bowen's/BCC [91—4].

It remains unclear whether MAL-PDT is less painful, as often stated, than ALA-PDT, due to differences in comparison studies between application times, site and type of lesions treated, and small study numbers. In a recent comparison of ALA and MAL in PDT for NMSC, both applied for 4 hours, MAL-PDT was less painful on the head but not on the trunk and extremities [95]. 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, 96].

Topical anaesthetics have not been shown to reduce pain significantly during PDT [97—99]. 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 SCC in-situ and BCC, although cooling may slow the photodynamic reaction [100]. Nerve blocks are useful for field treatments and have been shown to be more effective than cold air analgesia in a split-face study of MAL-PDT for multiple scalp AK [101—3].

Erythema and oedema are common post-PDT, with erosion, crust formation and healing over 2—6 weeks, but

ulceration is rare. Following PDT, localised photosensitivity can remain for up to 48 hours, ALA degrading with a half-life of about 24 hours, and MAL-induced PpIX clearing from normal skin within 24—48 hours [104—105]. Post-inflammatory hypo and hyper-pigmentation are rarely observed, probably less likely if treated sites are protected from strong sunlight in the days following treatment. A clinically obvious scar is rarely observed following PDT.

The risk of sensitization to ALA and MAL are reported, but overall appears uncommon, more likely in patients receiving multiple treatments over large areas [100—103].

Summary

Topical Photodynamic therapy (PDT) has been extensively studied since its initial description of the treatment 25 years ago. There is a substantial evidence base supporting its use in actinic keratoses, squamous cell carcinoma in-situ, superficial and certain thin low risk nodular basal cell carcinomas. The potential of field PDT therapy to delay/prevent new lesion formation is gradually accumulating evidence, with potential for immunocompetent but especially immunosuppressed patients. Additional studies beyond current cancer indications emphasize that this is a therapy platform, with potential in certain inflammatory and infective dermatoses as well as for photorejuvenation. The cosmetic benefits of PDT are well recognized, but novel approaches reviewed in this update, especially daylight PDT is helping overcome one of the challenges of large area PDT, namely treatment associated pain. New formulations of photosensitizers now provide therapy choice and efficacy comparisons and a large number of light sources are now available for delivery of conventional PDT in the clinic. Attention to protocol remains important in ensuring optimal efficacy, but topical PDT is now widely practised. ■

Литература

- Braathén Lasse R., Szeimies Rolf M., Basset Se-guin N. et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. *J Am Acad Dermatol*, 2007; 56: 125—43.
- Morton C.A., McKenna K.E., Rhodes L.E. Guidelines for topical photodynamic therapy *Br J Dermatol* 2008; 159: 1245—66.
- Morton C.A., Szeimies R.-M., Sidoroff A. and Braathén L.R., European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications — actinic keratoses, Bowen's disease, basal cell carcinoma. *J EADV* 2013; 27: 536—544.
- Morton C.A., Szeimies R.-M., Sidoroff A. and Braathén L.R., European guidelines for topical photodynamic therapy part 2: emerging indications — field cancerization, photorejuvenation and inflammatory/infective dermatoses. *J EADV* 2013; 27: 672—679.
- Dragieva C., Hafner J., Dummer R. et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation* 2004; 77: 115—21.
- 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—8.
- Henderson B.W., Dougherty T.J. How does photodynamic therapy work? *Photochem Photobiol* 1992; 55: 145—57.
- Maisch T., Moor A.C., Regensburger J. et al. Intense pulse light and 5-ALA PDT: phototoxic effects in vitro depend on the spectral overlap with protoporphyrin IX but do not match cut-off filter notations. *Lasers Surg Med*. 2011; 43: 176—82.
- 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-aminolaevulinic acid cream and placebo. *Br J Dermatol* 2012; 166: 137—46.
- Szeimies R.M., 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—94.
- Wiegell S.R., Wulf H.C., Szeimies R.-M., Basset-Se-guin N., Bissonnette R., Gerritsen M.-J.P., Gilaberte Y., Calzavara-Pinton P., Morton C.A., Sidoroff A. and Braathén L.R. Daylight photodynamic therapy for actinic keratosis: an international consensus. *J EADV* 2012; 26: 673—679.
- Neittaanmäki-Perttu N., Karppinen T.T., Grönroos M., Tani T.T., Pölonen I., Snellman E. Daylight photodynamic therapy for actinic keratoses: A randomized double-blinded non-sponsored prospective study comparing BF-200 aminolaevulinic acid with methyl-5-aminolaevulinic acid *Br J Dermatol*. 2014 Aug 11. doi: 10.1111/bjd.13326. [Epub ahead of print]
- Ibbotson S.H., Ferguson J. Ambulatory photodynamic therapy using low irradiance inorganic light-emitting diodes for the treatment of non-melanoma skin cancer: an open study. *Photodermatol Photoimmunol Photomed*. 2012; 28: 235—9.
- Fritsch C.J., Ruzicka T. Fluorescence diagnosis and photodynamic therapy in dermatology from experimental state to clinic standard methods *Envtl Path, Tox & Oncol* 2006; 25: 425—39.

15. Neus S., Ambichler T., Bechara F.G., Wohl S., Lehmann P. Preoperative assessment of basal cell carcinoma using conventional fluorescence diagnosis *Arch Derm Res* 2009; 301: 289—94.
16. Lee C.Y., Kim K.H., Kim Y.H. The efficacy of photodynamic therapy in delineating the lateral border between a tumour and a tumour-free area during Mohs micrographic surgery *Dermatologic Surgery* 2010; 36: 1704—10.
17. Tyrrell J.S., Campbell S.M., Curnow A. The relationship between protoporphyrin IX photobleaching during real-time dermatological methyl-aminolevulinic photodynamic therapy (MAL-PDT) and subsequent clinical outcome *Lasers Surg Med*; 2010; 42: 613—9.
18. Wiegell S.R., Skiveren P.A., Philipsen P.A. and Wulf H.C. Pain during photodynamic therapy is associated with protoporphyrin IX fluorescence and fluence rate. *Br J Dermatol* 2008; 158: 727—33.
19. <http://www.medicines.org.uk/emc/medicine/11913/SPC> accessed 11/11/14
20. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002204/WC500120044.pdf accessed 11/11/14
21. <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1356931026870.pdf> . accessed 01/10/14
22. <http://www.dusapharma.com/kerastick.html> accessed 11/11/14.
23. http://www.galderma.com.au/Portals/4/Pis%20and%20Cmis/Metvix%20cream_Pi%20_140826.pdf accessed 11/11/14.
24. Cochrane C., Mordon S.R., Lesage J.C., Koncar V. New design of textile light diffusers for photodynamic therapy. *Mater Sci Eng C Mater Biol Appl*. 2013; 33: 1170—5.
25. de Bruijn H.S., Meijers C., van der Ploeg-van den Heuvel A. et al. Microscopic localisation of protoporphyrin IX in normal mouse skin after topical application of 5-aminolevulinic acid or methyl 5-aminolevulinic acid *J Photochem Photobiol B*. 2008; 92: 91—7.
26. de Vijlder H.C., Sterenborg H.J., Neumann H.A., Robinson D.J. de Haas ER. Light fractionation significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial. *Acta Dermato-Venereologica*. 2012; 92: 641—7.
27. de Haas ER, Sterenborg HJ, Neumann HA, Robinson DJ. Response of Bowen disease to ALA-PDT using a single and a 2-fold illumination scheme. *Arch Dermatol* 2007; 143: 264-5.
28. de Haas E.R., de Vijlder H.C., Sterenborg H.J. 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—30.
29. Sotiriou E., Apalla Z., Chovarada 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.
30. Mosterd K., Thissen MRTM, Nelemans P. et al. Fractionated 5-aminolevulinic 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—70.
31. Szeimies R.M., Stockfleth E., Popp G. et al. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolevulinic acid patch: 12 months data. *Br J Dermatol* 2010; 162: 410—4.
32. Tschien E.H., Wong D.S., Pariser D.M. et al. The Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolevulinic 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.
33. Morton C., Campbell S., Gupta G. et al. Intraindividual, right-left comparison of topical methyl aminolevulinic acid-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; 155: 1029—36.
34. Piacquadio D.J., Chen D.M., Farber H.F. et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded phase 3 multicenter trials. *Arch Dermatol* 2004; 140: 41—6.
35. Dirschka T., Radny P., Dominicus R. et al. Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolevulinic acid for the treatment of actinic keratosis. *Br J Dermatol*, 2013; 168: 825—836.
36. Hauschild A., Stockfleth E., Popp G. et al. Optimization of photodynamic therapy with a novel self-adhesive 5-aminolevulinic acid patch: results of two randomized controlled phase III studies *Br J Dermatol*. 2009; 160: 1066—1074.
37. Wiegell S.R., Haedersdal M., Philipsen P.A. 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—6.
38. Wiegell S.R., 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 aminolevulinic acid in patients with multiple thin actinic keratoses of the face and scalp *Br J Dermatol* 2011; 164: 1083—90.
39. Wiegell S.R., 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—32.
40. Wiegell S.R., Fabricius S., Heydenreich J. et al. Weather conditions and daylight-mediated photodynamic therapy: protoporphyrin IX-weighted daylight doses measured in six geographical locations. *Br J Dermatol* 2013; 168: 186—91.
41. Sotiriou E., Apalla Z., Chovarada E. Panagiotidou D., Ioannides D. Photodynamic therapy with 5-aminolevulinic acid in actinic cheilitis: an 18 month clinical and histological follow-up. *J Eur Acad Dermatol Venereol* 2010; 24: 916—20.
42. Berking C., Herzinger T., Flaig M.J. et al. The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study of 15 patients. *Dermatol Surg* 2007; 33: 825—30.
43. Calzavara-Pinton P.G., Rossi M.T., Sala R. et al. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinic acid (MAL-PDT) in 20 Italian dermatology departments. Part 2: Oncologic and infectious indications. *J Photochem Photobiol Sci*. 2013; 12: 158—165.
44. 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—92.
45. http://www.euroderm.org/images/stories/guidelines/guideline_Management_Actinic_Keratosis-update2011.pdf accessed 11/11/14.
46. De Berker D., McGregor J., Hughes B. Guidelines for the management of actinic keratosis. *Br J Dermatol*, 2007; 156: 222—230.
47. Morton C.A., 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—35.
48. Lehmann P. Methyl aminolevulinic acid-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; 156: 793—801.
49. Calzavara-Pinton P.G., Venturini M., Sala R. et al. Methylaminolevulinic acid-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. *Br J Dermatol* 2008; 159: 137—44.
50. Truchuelo M., Fernandez-Guarino M., Fleta B. et al. Effectiveness of photodynamic therapy in Bowen's disease: an observational and descriptive study in 51 lesions. *J Eur Acad Dermatol Venereol* 2012; 26: 868—74.
51. Cavicchini S., Serini S.M., Fiorani R. et al. Long-term follow-up of methyl aminolevulinic acid (MAL)-PDT in difficult-to-treat cutaneous Bowen's disease. *Int J Dermatol* 2011; 50: 1002—5.
52. Lopez N., Meyer-Gonzalez T., Herrera-Acosta E. et al. Photodynamic therapy in the treatment of extensive Bowen's disease. *J Dermatolog Treat* 2012; 23: 428—30.
53. Morton C.A., Whitehurst C., McColl J.H. et al. Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. *Arch Dermatol* 2001; 137: 319—24.
54. Morton C.A., Birnie A.J., Eedy D.J. British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in situ (Bowen's disease) 2014. *Br J Dermatol* 2014; 170: 245—60.
55. Basset-Séguin N., Ibbotson S.H., Emtestam L. et al. Topical methyl aminolevulinic acid photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial *Eur J Dermatol* 2008; 18: 547—53.
56. Szeimies R., Ibbotson S., Murrell D. et al. A clinical study comparing methyl aminolevulinic acid 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.
57. Rhodes L.E., de Rie M., Enstrom Y. et al. Photodynamic therapy using topical methyl aminolevulinic acid vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol* 2004; 140: 17—23.
58. Rhodes L.E., de Rie M.A., Leifsdottir R. et al. Five year follow up of a randomized prospective trial of topical methyl aminolevulinic acid-photodynamic therapy versus surgery for nodular basal cell carcinoma. *Arch Dermatol*, 2007; 143, 1131—1136.
59. Foley P., Freeman M., Menter A. et al. Photodynamic therapy with methyl aminolevulinic acid for primary nodular basal cell carcinoma: results of two randomized studies *Int J Dermatol* 2009; 48: 1236—45.
60. 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.
61. Wiegell S.R., Skødt V., Wulf H.C. Daylight-mediated photodynamic therapy of basal cell carcinomas — an explorative study. *J Eur Acad Dermatol Venereol*. 2013. doi: 10.1111/jdv.12076.

62. Peng Q., Warloe T., Berg K. et al. 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. *Cancer* 1997; 79: 2282—308.
63. Morton C.A., Whitehurst C., McColl J.H., Moore J.V., MacKie R.M. Photodynamic therapy for basal cell carcinoma — Effect of tumour thickness and duration of photosensitizer application on response. *Arch Dermatol*, 1998, 134, 248—9.
64. Vinciullo C., Elliott T., Francis D. et al. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; 152: 765—72.
65. Arits A.H., Mosterd K., Essers B.A. et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncology*. 2013; 14: 647—54.
66. Loncaster J., Swindell R., Slevin F. et al. Efficacy of photodynamic therapy as a treatment for Gorlin Syndrome-related basal cell carcinomas. *Clinical Oncology* 2009; 21: 502—8.
67. http://www.euroderm.org/images/stories/guidelines/guideline_Basal_Cell_Carcinoma-update2012%20.pdf Last accessed 01/10/14.
68. Telfer N., Colver G. and Morton C. Guidelines for the management of basal cell carcinoma. *Br J Dermatol*, 2008; 159: 35—48.
69. Dragieva C., Prinz B.M., Hafner J. et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol* 2004; 151: 196—200.
70. Piaserico S., Belloni Fortina A., Rigotti P. et al. Topical photodynamic therapy of actinic keratosis in renal transplant patients. *Transplant Proc* 2007; 39: 1847—50.
71. Perrett C.M., McGregor J.M., Warwick J. et al. Treatment of post-transplant premalignant skin disease: A randomized inpatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007; 156: 320—8.
72. 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.
73. Wulf H.C., 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.
74. Wennberg A.M., Stenquist B., Stockfleth E. et al. Photodynamic therapy with methyl aminolaevulinate for prevention of new lesions in transplant recipients: a randomized study. *Transplantation* 2008; 86: 423—9.
75. 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.
76. Willey A., Mehta S., Lee P.K. Reduction in incidence of squamous cell carcinoma in solid organ transplant recipients treated by cyclic Photodynamic therapy. *Dermatol Surg* 2010; 36: 652—8.
77. Braathen L., Morton C., Basset-Seguín 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—6.
78. Basset-Seguín N., Baumann Conzett K., Gerritsen MJP, et al. Photodynamic therapy for actinic keratoses in organ transplant recipients. *J Eur Acad Dermatol Venereol* 2013; 27: 57—66.
79. Apalla Z., Sotiriou E., Chovarda E., Lefaki I., Devliotou-Panagiotidou D. and 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.
80. Bagazgoitia L., Cuevas Santos J., Juarraz 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—15;
81. Szeimies R.M., 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—9.
82. Edstrom D.W., Porwit A., Ros A.M. Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: clinical and histological response. *Acta Derm Venereol* 2001; 81: 184—8.
83. Zane C., Venturini M., Sala R., Calzavara Pinton P. Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unifoliate cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed* 2006; 22: 254—8.
84. Fernandez-Guarino M., Harto A., Perez-García B., Montull C., De Las Heras E., Jaen P. Plaque-phase mycosis fungoides treated with photodynamic therapy: results in 12 patients. *Actas Dermosifilogr* 2010; 101: 785—91.
85. Kim S.T., Kang D.Y., Kang J.S., Baek J.W., Jeon Y.S., Suh K.S. Photodynamic Therapy with Methyl-aminolaevulinic Acid for Mycosis Fungoides. *Acta Derm Venereol* 2012; 92: 264—8.
86. Quéreux G., Brocard A., Saint-Jean M. et al. Photodynamic therapy with methyl-aminolevulinic acid for paucifoliate mycosis fungoides: A prospective open study and review of the literature. *J Am Acad Dermatol*. 2013; 69: 890—7.
87. Paoli J., Ternesten Bratel A., Lowhagen G-B et al. Penile intraepithelial neoplasia: results of photodynamic therapy. *Acta Derm Venereol* 2006; 86: 418—21.
88. Shieh S., Dee A.S., Cheney R.T. et al. Photodynamic therapy for the treatment of extramammary Paget's disease. *Br J Dermatol* 2002; 146: 1000—5.
89. 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—6.
90. Zawislak A.A., McCarron P.A., McCluggage W.G. et al. Successful photodynamic therapy of vulval Paget's disease using a novel patch-based delivery system containing 5-aminolaevulinic acid. *Br J Obstet Gynaecol* 2004; 111: 1143—5.
91. Grapengiesser S., Ericson M., Gudmundsson F. et al. Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol* 2002; 27: 493—497.
92. 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.
93. Warren C.B., Karai L.J., Vidmos A., Maytin E.V. Pain associated with aminolevulinic acid-photodynamic therapy of skin disease. *J Am Acad Dermatol* 2009; 61: 1033—1043.
94. Halldin C.B., 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.
95. Gaal M., Otrósinka S., Baltas E. et al. Photodynamic therapy of nonmelanoma skin cancer with methyl aminolaevulinate is associated with less pain than with aminolaevulinic acid. *Acta Derm Venereol* 2012; 92: 173—175.
96. 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.
97. Holmes M., Dawe R.S., Ferguson J., Ibbotson S.H. 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.
98. Langan S.M., Collins P. Randomized, double-blind, placebo-controlled prospective study of the efficacy of topical anaesthesia with a eutectic mixture of lignocaine 2.5% and prilocaine 2.5% for topical 5-aminolaevulinic acid-photodynamic therapy for extensive scalp actinic keratoses. *Br J Dermatol* 2006; 154: 146—149.
99. Skiveren J., Haedersdal M., Philipsen P.A. et al. Morphine gel 0.3% does not relieve pain during topical photodynamic therapy: a randomized double-blind, placebo controlled study. *Acta Derm Venereol* 2006; 86: 409—411.
100. 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.
101. Paoli J., Halldin C., Ericson M.B., Wennberg A.M. Nerve blocks provide effective pain relief during photodynamic therapy for extensive facial actinic keratoses. *Clin Exp Dermatol* 2008; 33: 559—564.
102. Halldin C.B., Paoli J., Sandberg C., Gonzalez H., Wennberg A.M. 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.
103. 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.
104. Golub A.L., Gudin D.E., Kennedy J.C. 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.
105. Angell-Peterson E., Christensen C., Mullet C.R., Warloe T. Phototoxic reaction and porphyrin fluorescence in skin after topical application of methyl aminolaevulinate. *Br J Dermatol* 2006; 156: 301—307.
106. Wulf H.C., 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.
107. Harries M.J., Street G., Gilmour E. et al. Allergic contact dermatitis to methyl aminolaevulinate (Metvix) cream used in photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2007; 23: 35—36.
108. Hohwy T., Andersen K.E., Solvsten H., Sommerlund M. Allergic contact dermatitis to methyl aminolaevulinate after photodynamic therapy in 9 patients. *Contact Derm* 2007; 57: 321—323.
109. Korshoj S., Solvsten H., Erlandsen M., Sommerlund M. Frequency of sensitization to methyl aminolaevulinate after photodynamic therapy. *Contact Derm* 2009; 60: 320—324.