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REVIEW ARTICLE

Daylight photodynamic therapy with MAL cream for large-scale photodamaged skin based on the concept of 'actinic field damage': recommendations of an international expert group

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Abstract

Conventional PDT (c-PDT) is a widely used and approved non-invasive treatment for actinic keratosis (AK). Recent clinical, histological and immunohistochemical observations have shown that c-PDT with methyl aminolevulinate (MAL) may also partially reverse the signs of photodamage. However, pain and the need for special light source equipment are limiting factors for its use, especially in the treatment of large areas. More recently, daylight PDT (DL-PDT) has been shown to be similar to c-PDT in the treatment of AK, nearly painless and more convenient to perform. To establish consensus on recommendations for the use of MAL DL-PDT in patients with large-scale photodamaged skin. The expert group was comprised of eight dermatologists. Consensus was developed based on the personal experience of the experts in c-PDT and DL-PDT, and results of an extensive literature review. MAL DL-PDT for large areas of photodamaged skin was evaluated and recommendations based on broad clinical experience were provided. As supported by evidence-based data from multicentre studies conducted in Australia and Europe, the authors defined the concept of 'actinic field damage' which refers to photodamage associated with actinic epidermal dysplasia, and provide comprehensive guidelines for the optimal use of DL-PDT in the treatment of actinic field damage. The authors concluded that MAL DL-PDT has a similar efficacy to c-PDT at 3-month (lesion complete response rate of 89% vs. 93% in the Australian study and 70% vs. 74% in the European study (95% C.I. = [−6.8;−0.3] and [−9.5;2.4] respectively) and 6-month follow-ups (97% maintenance of complete lesion response) in the treatment of AKs. The authors agree that DL-PDT is not only efficacious but also nearly pain-free and easy to perform, and therefore results in high patient acceptance especially for the treatment of areas of actinic field damage.
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Conflicts of interest

Dr. WG Philipp-Dormston (Germany) is a member of the scientific advisory boards of Allergan, Biofrontera, Galderma and Leo Pharma, holds lectures and conducts clinical studies for these companies. Dr. G Sanclemente (Colombia) has received speakers' honoraria and financial support for attending meetings from Galderma, and conducts clinical studies with products from this pharmaceutical lab. Dr. L Torezan (Brazil) is a member of an international advisory board of Leo Pharma and consultant for Galderma. Dr. MT Clementoni (Italy) is a member of the scientific advisory boards of Lumenis Ltd, Lutronic Ltd, Quanta System and Galderma and holds lectures, conducts clinical studies and did clinical trainings for these companies. Dr. A Le Pillouer Prost (France) is a member of the scientific advisory boards of DEKA, Genèvrier, Galderma and Merz, has received honoraria as consultant and has participated from these firms in clinical studies. Dr. H Cartier (France) is a member of the scientific advisory board of Galderma, receives honoraria for lectures and has participated as trial investigator in numerous licensing studies. Prof. RM Szeimies (Germany) is a member of the scientific advisory boards of Biofrontera, Galderma and Leo Pharma, receives honoraria from these firms for lectures and has participated as

trial investigator in numerous licensing studies in the field of dermato-oncology. Dr. P Bjerring (Denmark) is a member of the scientific advisory boards of Galderma and Fertin Pharma.

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Introduction

Photodamage is considered to be the structural and functional deterioration of chronically sun-exposed skin, resulting in altered skin texture, tightness and thickness, pale skin, dyschromia, wrinkles, telangiectasias, erythema, sebaceous gland hypertrophy and epithelial atypia or dysplasia.[1,2] When patients present with photodamaged skin along with a past medical history of at least one actinic keratosis (AK) and/or non-melanoma skin cancer (NMSC), we propose this cluster of alterations to be referred to as actinic field damage.

Multiple therapeutic approaches have been described to treat signs of photodamaged skin.[3] It is commonly agreed that prevention through avoidance of exposure to ultraviolet (UV) light is key. Progression can be decreased by sunscreen use, though adherence is an issue.[4] Non- or minimally invasive procedures such as superficial peelings, microdermabrasion, non-ablative lasers, radiofrequency devices, mesotherapy or microneedling usually show low efficacy and require multiple sessions, whereas more invasive approaches are associated with longer downtimes and possibly increased risk of adverse events (AEs).[5,6] Topical therapies including imiquimod, ingenol mebutate and 5-fluorouracil are being used as field-directed therapies for AK, though lesion recurrence in the long term remains a concern.[7] Although fractionated ablative laser treatment shows satisfactory results, it requires costly equipment, training and extensive user experience, along with lack of selectivity and thus efficacy in treating the dysplastic keratinocytes of actinically damaged skin.[8] The need for selective targeting of the epidermal actinic damage, as well as the indirect secondary effects on dermal actinic damage, make daylight photodynamic therapy (DL-PDT) an effective, safe and easy option for the treatment of photodamaged skin.[9]

Materials and methods

The international expert group was comprised of eight dermatologists. Consensus was developed after discussion, based on the personal experience of the experts in conventional PDT (c-PDT) and DL-PDT, and results of an extensive literature review are presented.

Results

Methyl aminolevulinate (MAL) DL-PDT for large areas of photodamaged skin was evaluated and consensus was reached between the experts for several recommendations detailed hereafter.

Continuum between photodamage, AK and squamous cell carcinoma: introducing the concept of 'actinic field damage'

The UV-induced deleterious skin effects start their continuum with the well-studied DNA mutations in the p53 gene. This molecular damage leads to keratinocyte morphologic changes and mutated clone cells that tend to be subclinical at early stages.[10]

In the mid- and long term, several contributors such as reactive oxygen species, degraded dermal collagen, abnormal elastic fibres, and alterations in microvasculature such as regression of small blood vessels and neo-angiogenesis lead to subtle patches in the skin which progressively extend to visible photodamage features (tactile roughness, sallowness, wrinkles, telangiectasia, etc.) or dysplastic keratinocytes (AK) and/or squamous cell carcinoma (SCC) of the skin.[11]

The term 'field cancerization,' first introduced by Slaughter in 1953, was based on 'tumour multiplicity' and all the changes encountered beyond most oral squamous cell tumours.[12] This term has also been used for neoplasms of the skin where it describes the presence of multilocular clinical and subclinical neoplastic lesions and dysplastic keratinocytes multiplicity in UV-exposed areas.[13,14] Photodamaged skin, however, also displays multiple subclinical and clinical alterations, not necessarily related to skin tumours, at least in early stages.[15] Therefore, the authors propose the concept of actinic field damage. This refers to chronically UV-exposed skin with DNA alterations, such as p53 mutations that predispose to or that is accompanied by at least one AK or NMSC.

Conventional PDT for the treatment of AK

Daylight photodynamic therapy is a widely used and approved non-invasive treatment for AK. Two products are currently in use: 5-aminolevulinic acid (5-ALA) and its methyl esther, MAL. 5-ALA is hydrophilic with limited ability to penetrate tissues, whereas MAL's lipophilic properties facilitate tissue penetration, providing enhanced target-cell specificity.[16,17] Use of 5-ALA and MAL in AK requires incubation with occlusion for several hours, followed by exposure of the treated area to an appropriate light source.[17,18]

Current European Guidelines support c-PDT as an effective and safe treatment for AK (Strength of Recommendation A, Quality of Evidence I) with typical clearance rates of 89–92% for thin and moderate thickness AK on the face and scalp 3 months after therapy.[13] These guidelines highlight the benefits of individual lesion treatment as well as the need for treatment of larger fields to treat subclinical lesions and improve cosmetic outcomes.

The effect of c-PDT in the case of classic 'field cancerization' has also been investigated (Strength of recommendation B, Quality of evidence I). It underlines the unique potential of PDT observed in previous findings regarding the prevention of NMSC in murine models[19–23] and in immunosuppressed as well as immunocompetent patients,[14,24–28] resulting in publications primarily focused on the use of c-PDT for NMSC field treatment.[29,30]

Beyond the treatment and prevention of AK and NMSC with c-PDT, MAL c-PDT also reverses the signs of actinic skin damage and photoageing by decreasing the severity and extent of keratinocyte atypia associated with dermal collagen deposition.[11] Moreover, it improves solar elastosis with a decreased expression of tumour protein p53 (TP-53) (Fig. 1) and elevated levels of procollagen-I, matrix metalloproteinase-1 and Tenascin-C.[11,31–33]

However, c-PDT has certain limitations and difficulties for its utilization due to the need of specific light sources and occlusion for several hours. Use of c-PDT is also limited particularly in treatments based on the term 'actinic field damage' due to the pain experienced by patients during illumination which often requires a multimodal pain management strategy.[34–38]

DL-PDT with MAL cream for AKs

Methyl aminolevulinate-PDT using natural daylight (MAL DL-PDT) as the illumination source was first described in 2008, followed by studies showing that DL-PDT is as effective as c-PDT for the treatment of AKs, nearly painless, safer and more cost-effective than c-PDT.[39,40] The initial trial, comparing DL-PDT with c-PDT for the treatment of facial and scalp AK, showed similar efficacy for both procedures in clearing AKs, with significant lower pain scores of 2.0 (SD ± 1.9) vs. 6.7 (SD ± 2.2) for DL-PDT and c-PDT, respectively, on the numerical rating scale (0–10).[39] Uninterrupted light exposure for 2 h is required to continuously produce and activate PpIX within the targeted cells, resulting in a constant microphototoxic environment within the cells.[39] Although sunny weather is not mandatory for PpIX activation, DL-PDT is not recommended on rainy days or temperatures below 10 °C or higher than 35 °C.[41–43]

Two recent phase III studies performed in Australia and Europe confirmed that MAL DL-PDT is as efficacious as c-PDT, leads to fewer related AEs, is nearly painless and more convenient for patients.[40,44] At week 12 after a single DL-PDT session, the lesion complete response rate with DL-PDT was non-inferior to c-PDT: about 89% vs. 93% in the Australian study and 70% vs. 74% in the European study (95% C.I. = [−6.8;−0.3] and [−9.5;2.4] respectively). The phase III Australian study also showed a high maintenance of complete lesion response 6 months after a single treatment session in both the DL-PDT and c-PDT treatment groups (about 97% on average).[40] In the above-mentioned phase III studies, treatment efficacy was observed regardless of weather conditions.

Methyl aminolevulinate, unlike 5-ALA, has been extensively studied in DL-PDT for the treatment of AK. Topical application of the photosensitizer is performed immediately after pretreatment. MAL is applied to the affected area (field of actinic damage) at a dose of 1–2 g per face or area, without the need for occlusion.

An organic sunscreen should be applied to the entire DL-PDT treatment area and to all other sun-exposed areas before application of the photosensitizer to protect from UV exposure. After 2 h of daylight exposure, patients are requested to remove any remaining MAL cream and remain indoors the rest of the day to prevent further photodynamic reaction, avoiding sun exposure for 2 days following treatment.

C-PDT in actinic field damage

The rejuvenating effects of PDT on photoaged skin have been well-documented in several preclinical and clinical trials,[11,21,31–34,45–47] and have been recently reviewed by an expert group for aesthetic PDT.[48] Besides the clearance and prevention[24] of AK, an improved skin texture (tactile roughness), pale skin, wrinkles,

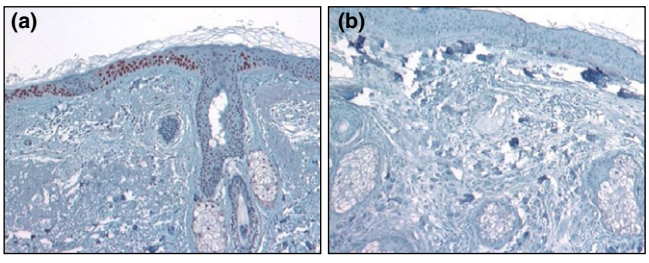

Figure 1 P53 expression in sun damaged skin (a) before and (b) after methyl aminolevulinate conventional Photodynamic therapy. Pictures from Drs L. Torezan and R.M. Szeimies.

mottled pigmentation, dyspigmentation (including solar lentigines), facial erythema and elastosis were demonstrated in most studies after c-PDT. The authors also commented that c-PDT for photorejuvenation with light-emitting diode red light sources can require specific pain management.

Advantages of DL-PDT for the treatment of actinic field damage

Based on the concept of actinic field damage, DL-PDT appears to be the ideal option for the unmet need of a convenient yet effective treatment. As for c-PDT, it is characterized by a combination of selective keratinocyte uptake and cytotoxicity as well as indirect cytokine-mediated dermal effect, as illustrated in Fig. 2.[21,31,46,47] Representative photographs of patients treated with DL-PDT are shown in Fig. 3. The objective of DL-PDT for actinic field damage is the reduction in visible photodamage as well as the selective treatment of subclinical lesions, the treatment of AKs and the prevention of AK formation and eventually progression into NMSC.[24]

Daylight photodynamic therapy could be a complementary and convenient treatment option to already existing rejuvenation procedures for patients with actinic field damage. It can be performed throughout the year in certain regions of the world such as Australia, Latin America and South Europe and from March/April to September/October in Northern Europe, and under all weather conditions where they are suitable to stay comfortably outdoors for 2 h (except rain).[49]

Synergistic therapies and pretreatment procedures to enhance photosensitizer uptake

Similar to c-PDT, pretreatment of the skin prior to DL-PDT is recommended to ensure sufficient uptake of the photosensitizer. Actinic field damage pretreatment is gentle and includes the entire area (not lesion by lesion). The authors propose that as long as the efficacy enhancement of the pretreatment procedure is restricted to stratum corneum alterations and mainly due to an increased drug delivery and epidermal reorganization, the term 'intensified PDT' is appropriate (Fig. 4). In case of a direct deep dermal effect in terms of tissue stimulation through dermal injury and neocollagenesis, one should use the term 'synergistic PDT.' This is because the effect is not solely based on the photodynamic reaction, but on the combination of both therapies.

Gentle curettage is a well-known pretreatment procedure for thin AKs.[13] Sandpaper is a low-cost and easy procedure, which is especially suitable for large areas like the face, décolleté or back of the hands.[50–52] Similar to sandpaper, microdermabrasion (crystal or water microdermabrasion) is easy to use particularly when large areas are to be treated.[53–56]

Mild chemical peelings (α-hydroxy acid or salicylic acid) can be used to reduce stratum corneum thickness. However, physicians should be cautious due to the possible interaction of the acids with the photosensitizer and possible formation of denatured stratum corneum which will interfere with penetration. Hence, it is advisable that pretreatment is carried out at least 3 days before DL-PDT.[57]

Microneedling (roller or stamp needling) is a procedure used for aesthetic indications as well as in combination with PDT for the treatment of AKs and NMSC, and therefore appears to be an appropriate option for DL-PDT pretreatment of actinic field damage.[58,59] Depending on the length of the needle, this pretreatment can be used to facilitate the penetration of the photosensitizer as an intensified procedure (250−500 μm needle) or as a synergistic procedure regarding the stimulation of collagen

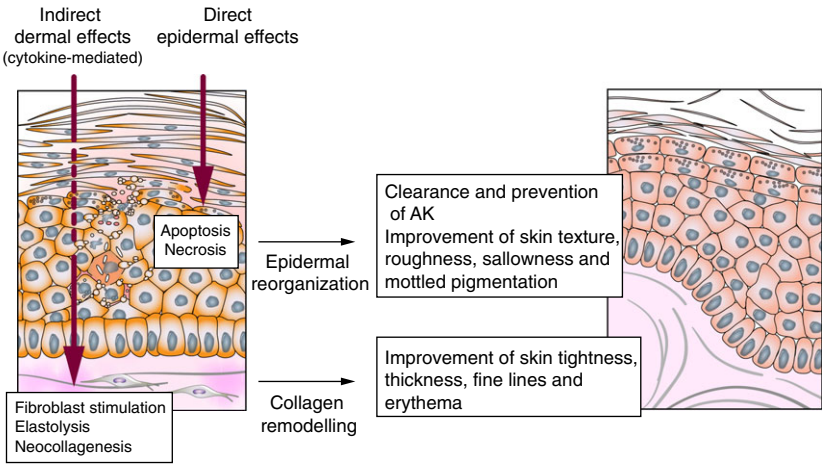

Figure 2 Methyl aminolevulinate daylight photodynamic therapy induces epidermal reorganization and indirect dermal effects in the concept of 'actinic field damage'.

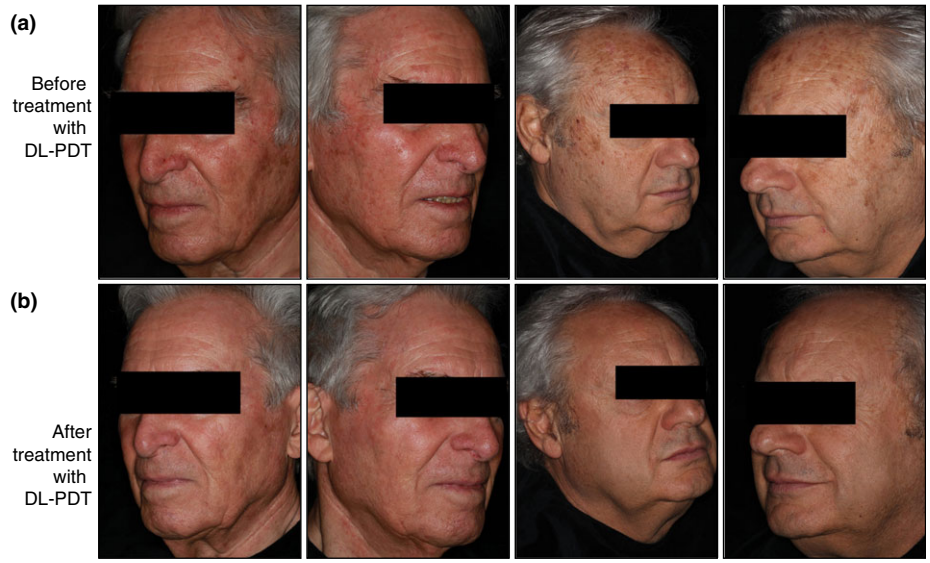

Figure 3 Clinical photographs of patients (a) before and (b) after treatment with daylight photodynamic therapy (DL-PDT; courtesy of Dr M. Tretti Clementoni).

biosynthesis (1000−2000 μm needle). Needling should be performed immediately after application of the sensitizer to prevent the flow of blood and tissue fluids into the needle channels which may hamper penetration of the sensitizer.[58] Deeper needling has the disadvantage of being painful and therefore often requires topical analgesia which can lead to inadvertent interactions with the photosensitizer.[57]

Similarly microneedling for rejuvenation and depending on the settings (energy, density), ablative fractional lasers (AFL) (CO_2 or Er:YAG), can be used as an intensified procedure. This facilitates penetration and delivery of the sensitizer by altering the stratum corneum with low settings. By extrapolation from studies on AK we suggest about 5–10 mJ/cm² energy and 2–4% density for a fractional CO_2-laser,[60] and approximately 1.15 W, two stacked pulses, 50 μs and 7.4% density for a fractional Erbium-YAG-laser.[61] AFL systems can also be used as a synergistic procedure with higher settings providing deeper channels into the dermis.[61–63]

However, equipment and user experience may be limiting factors for this approach. In case higher performance parameters are used, pain management may be required immediately after daylight exposure and overnight, and prolonged posttreatment care, as well as downtime, should be taken into consideration. High densities of the channels should be avoided since the resulting tissue damage may interfere with the synthesis of PpIX.[64] More recently, a study demonstrated that AFL-pretreatment at low settings combined with DL-PDT had a high tolerability and increased efficacy compared to c-PDT and DL-PDT for difficult-to-treat AK in organ transplant recipients.[61]

Daylight exposure and photodynamic process

Patients are requested to expose the treated areas to daylight within 30 min after MAL application, according to the algorithm in Fig. 5. The continuous production and activation of PpIX during the 2 h of exposure to daylight is based on a steady-state photodynamic effect, unlike the 3-h accumulation of PpIX required for c-PDT that is followed by rapid activation, responsible for the pain during illumination.[39] Continuous activation of PpIX is key in pain management, especially when treating large areas as in the treatment of actinic field damage.

Posttreatment care

During the first 7–10 days, side-effects like erythema, blistering, sterile follicular pustules and crusting may occur. AEs such as infection or scaring are very rare even in the treatment of AK with c-PDT and are usually not expected when treating actinic field damage with DL-PDT. Immediately after the 2-h daylight exposure, cooling with thermal water sprays, physiologic saline compresses or cool pads may be used, although they are not mandatory. On the following days, use of neutral moisturizers may be used to minimize skin reaction. 'Intensified' or 'synergistic' procedures which directly target dermal structures require special posttreatment care. Follow-up visits should be scheduled on an individual basis depending on the degree of actinic damage, treatment area and pretreatment procedure. In all cases, strict sun protection is required after treatment (textile sun protection or SPF 50+ cream) to avoid posttreatment hyperpigmentation, and long-term sunscreen should be recommended.[65]

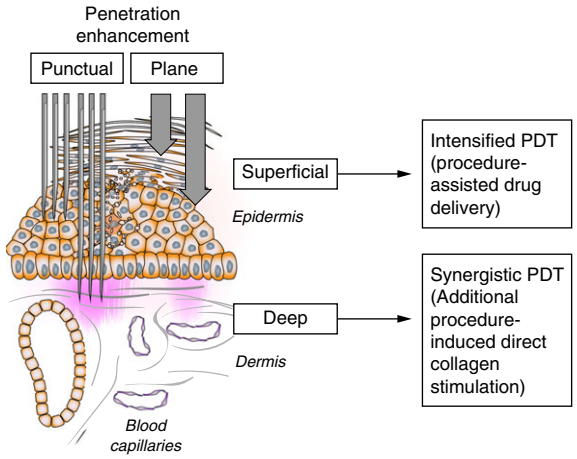

Figure 4 Principles of prelesional photodynamic therapy (PDT) treatment approaches and supportive procedures.

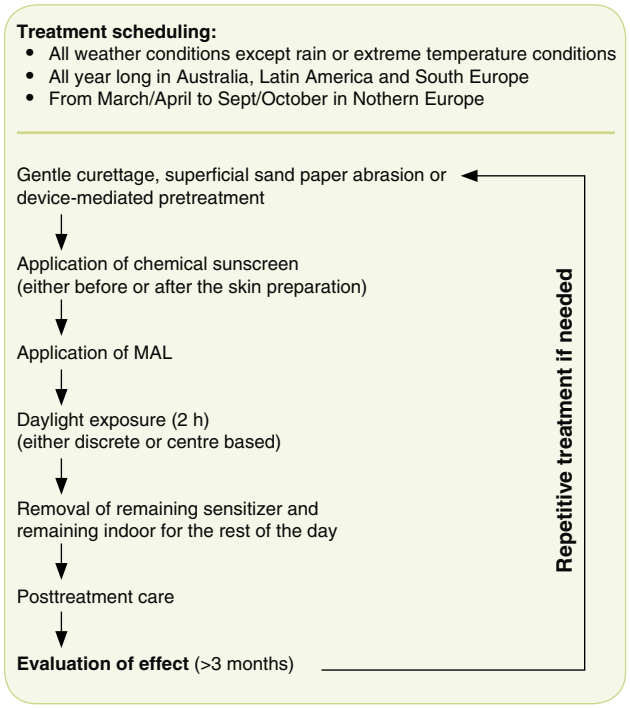

Figure 5 Algorithm for daylight photodynamic therapy of actinic field damage.

Treatment intervals

For DL-PDT in grade I and II AK, one session has been proved to be sufficient.[43] For other indications (photodamage or rejuvenation), there is not sufficient evidence to suggest an appropriate number of sessions. Depending on the degree of actinic damage in photodamage or rejuvenation, repeated sessions may be required.[34] A final evaluation of the therapeutic outcome should be performed at the earliest 3 months after treatment, respecting the required time for epidermal reorganization and in particular for indirect dermal effects like neocollagenesis.[9]

Conclusion

To propose the role for the treatment of photodamaged skin with DL-PDT, the authors have defined the concept of 'actinic field damage'. Based on the authors' clinical experience and extensive literature review, we concluded that MAL DL-PDT has a similar efficacy to c-PDT at 3- and 6-month follow-ups in the treatment of AKs. In addition, this procedure can be combined with an array of pretreatment procedures to obtain further intensified or synergistic effects. DL-PDT appears to be an effective, safe and nearly pain-free treatment approach in large-scale actinic damage.

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