JDDG
Journal of the German Society of Dermatology

Review

Submitted: 28.11.2012
Accepted: 26.3.2013

DOI: 10.1111/ddg.12119

Photodynamic therapy for skin rejuvenation: treatment options – results of a consensus conference of an expert group for aesthetic photodynamic therapy

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Summary

In addition to providing effective treatment for non-melanoma skin cancers or their precursors, photodynamic therapy (PDT) has also attracted considerable attention for its use on aesthetic dermatology. In a first consensus publication the mechanisms of action of its photorejuvenation effects and recent studies were presented; in this paper treatment protocols for the different anatomical regions exposed to chronic sun damage like face, neck, décolleté and the back of the hands are given and suitable procedures for pre- and after-care are discussed.

Introduction

Besides the well- documented effects of photodynamic therapy (PDT) in non-melanoma skin cancer and precursors such as actinic keratoses (AK), recently the use of PDT for skin rejuvenation has become popular primarily because of the excellent cosmetic results [1–8]. Within the context of a consensus conference of dermatologists involved in aesthetic photodynamic therapy on 02 December 2011 in Düsseldorf, Germany, current data on PDT for skin rejuvenation was reviewed and summarized. In the first of two papers the current studies on photodynamic skin rejuvenation and underlying molecular mechanisms of action were discussed [9]. In the following article concrete treatment recommendations for different anatomic sites of sun-damaged skin and suitable techniques for pre- and after-treatment will be discussed.

Prerequisites and pre-treatments

A dermatologic examination before the start of treatment to exclude possible tumors in the treatment area is mandatory. Determination and documentation of the degree of sun damage, e.g. with an evaluation scale (see also Table 3 in Karrer et al., [9]) before initiation of PDT is further important, especially as the approved and commercially available photosensitizers are not licensed for this indication and are employed

Table 1 Pre-treatments and combinations suitable for aesthetic PDT.

Procedure	Features
Chemical peeling	▸ Treatment *before* PDT ▸ Mild peeling with α-hydroxy acid (30–50 %) or salicylic acid (10–20 %) ▸ 4–5 peelings in intervals of 2–4 weeks up to maximally 3 days before PDT
Mechanical peeling	▸ Treatment *before* PDT ▸ Crystal or aqua microdermabrasion also possible immediately before application of sensitizer
Curettage	▸ Mild curettage particularly in keratotic lesions ***before*** application of sensitizer ▸ If indicated in combination with topical urea preparations (5–10 %) for 2 weeks before PDT
Ablative fractional lasers (Er:YAG, CO_2)	▸ Laser treatment ***before*** application of sensitizer ▸ Low power setting for penetration of the stratum corneum ▸ High power setting (channels up to a depth of 1,700 µm) for synergistic effects through stimulation of collagen biosynthesis
Microneedling	▸ Needling ***immediately after*** application of sensitizer ▸ Needle length 250–500 µm for facilitated penetration of the sensitizer ▸ Needle length 1,000–2,000 µm for synergistic stimulation of collagen biosynthesis
Botulinum toxin	▸ 2 weeks *before* PDT at the latest
Fillers	▸ 2 weeks *after* PDT at the earliest

in an off-label manner. Detailed information on mechanism of action and expected results is also recommended, possible risks and side effects should all be addressed. Precise photodocumentation of clinical findings with suitable equipment (perhaps UV photography) is helpful.

In all cases the patient should be informed about the necessity of adequate sun protection independent of the planned PDT and particularly when possible pre-treatments (laser, peeling, etc.) with the danger of postinflammatory hyperpigmentation are planned. The avoidance of strong sun exposure of the treated areas for several weeks after PDT should be discussed when timing the treatment (vacation, summertime). Special attention should be paid to possible other skin lesions, particularly epithelial tumors or their precursors, in the planned treatment areas. Planned photodynamic treatments should in such cases be oriented on the curative indication. Deviations from the approved treatment protocols could lead to increased recurrences or a lack of response and should therefore be avoided.

Pre-treatments can increase the efficacy of PDT both in curative as well as in aesthetic use (Table 1). On the one hand, they can synergistically support the treatment effect (e.g. self-stimulation of collagen biosynthesis) or, on the other hand, improve penetration of the photosensitizer (microneedling, fractional lasers, chemical/ mechanical peeling). They are not, however, absolutely necessary. Combination with other aesthetic procedures such as the use of botulinum toxin or fillers is possible. In analogy to laser treatment, the time interval of at least two weeks is recommended by the expert group--botulinum toxin should be used 2 weeks before PDT and fillers first 2 weeks after PDT. The pre-treatment protocols also vary greatly depending on location, skin type/ skin aging type and extent of extrinsic (particularly UV-induced) skin damage and are therefore discussed under the individual treatment zones.

PDT for aesthetic reasons is not as effective as highly invasive technique for the treatment of deep wrinkles; the expectations of the patients should therefore not be unrealistic. PDT can achieve an improvement of dyspigmentation, skin roughness, fine lines and complexion as well as an increase in skin smoothness and a reduction of actinic elastosis. The skin rejuvenating effect of PDT on sun-damaged skin is well-documented in diverse published clinical studies [1–8].

Treatment zone: face

Microneedling can be recommended for improvement of penetration of the photosensitizer. For example, needle rollers with needle lengths of 250 up to 1,500 µm can be employed. While shorter needle lengths between 250 and 500 µm facilitate the penetration of the photosensitizer through the stratum corneum, the longer needles (1,000–2,000 µm) can synergistically stimulate collagen biosynthesis through injury in the dermis [10]. Needling is painful and may require analgesia, watching for possible interactions with the photosensitizer. Needling immediately after application of the photosensitizer

has proved to be advantageous, as otherwise the flow of blood and tissue fluid into the needle channels immediately after needling can hamper penetration of the sensitizer [10]. Alternatively, microdermabrasion/ peeling (chemical/ mechanical) or pre-treatment with an ablative fractional laser system (CO_2 or Er:YAG laser) can be performed. In such cases pre-treatment should be performed *before* application of the photosensitizer. Usually parameters of the laser systems are employed that only facilitate the penetration of the stratum corneum. Higher performance parameters that produce deeper channels in the skin down into the dermis (1,700 µm), are also possible, as these parameters achieve additional synergistic effects [11]. Nevertheless, higher energy doses are also distinctively more painful requiring local anesthesia) and may also need further measures for herpes prevention (e.g. valacyclovir or acyclovir). Non-ablative fractional laser systems do not improve penetration [12]. Mild curettage of the treatment area, particularly with keratotic lesions, is also recommended as well as long-term (1–2 weeks) pre-conditioning with 5–10 % urea preparations or a mild peeling (α-hydroxy acid 30–50 % or salicylic acid 10–20 %; 4–5 peelings at intervals of 2–4 weeks up to maximally 3 days before PDT can lead to improvement. Mechanical peelings, such as crystal or aqua microdermabrasion, can be performed immediately before PDT (Table 1).

Because of the synergistic effects of pre-treatment and PDT, the expected phototoxic reactions can be markedly increased and thus the downtime (duration of being socially unpresentable) of the patient is prolonged.

In the case of coexistence of actinic keratoses, the application (thickness, occlusion) and the incubation time should be oriented on the parameters set for the individual photosensitizers licensed on the European market for field treatment.

Deviations from existing treatment protocols when treating only sun-damaged skin exist mainly with respect to the parameters incubation time and irradiation. Alterations of the sensitizer concentrations due to self-manufactured mixtures are not recommended based on possible incompatibilities (pH value, water content) that can result in reduced penetration. Data on aesthetic use of PDT are to date only available for Levulan Kerastick® (ALA) and Metvix® (MAL) licensed in the USA. Shorter incubation times than the stated 3 hours result in reduced synthesis of protoporphyrin IX, making irradiation less painful. Nonetheless, there is the possibility of further porphyrin synthesis after treatment, so that sun exposure can still induce a photodynamic reaction. Direct sun protection after treatment is therefore recommended for up to 48 hours.

The use of other light sources than those approved for PDT (red light of about 630 nm with a dose of 37 J/cm^2) is possible in principle. Besides the LED lamps at 630 nm or broad-spectrum lamps with corresponding filter systems, flashlamp-pumped, pulsed laser systems or flashlamps can be employed [13, 14]. The main advantage is less pain because of the shorter duration of light administration. Also, synergistic effects can be expected. The lack of standardization of power and application data for the individual systems is problematic. Particularly in patients with AK or epithelial tumors in the treatment areas, the uniform and overlapping application of light is essential; otherwise skipped areas may facilitate treatment failure or recurrences [14].

Pain during treatment

PDT is a painful therapeutic procedure. Characteristically, pain develops quickly after the start of irradiation, cumulates during irradiation and decreases again over several hours after irradiation. Persistence of pain over more than 48 hours is observed only very rarely. The pain sensation is dependent on factors such as location (most intense face/scalp), degree of previous sun damage, skin type, gender and disease present (AK more painful than basal cell carcinomas). It varies greatly individually and can be influenced. Due to induction by way of stimulation of free nerve endings in the epidermis during irradiation, the elimination of the sensation of pain during irradiation is difficult with classical analgetic agents. Cold in the form of cold dressings immediately before and after irradiation or in the form of cold air (e.g. Zimmer Cryo 6, Zimmer Medizinsysteme, Neu-Ulm, Germany, or Criojet Air, Crio Medizintechnik, Birkenfeld, Germany) before and during irradiation have been found to be favorable and harmless treatment options. Also local anesthetic blockades to eliminate pain (e.g. with ropivacaine) have proven useful, especially for the treatment of areas such as the scalp and face [15]. Intravenous analgesia with propofol is also possible, but requires monitoring of the patient. One possibility to impact pain and simultaneously improve oxygen supply in tissue during irradiation is fractioning, i.e. interruptions (e.g.) during the irradiation process are made, often with cooling during the pauses, so that the total dose of applied light remains equal, but the duration of treatment is increased. PDT for solely aesthetic indications in the lack of AK is usually less painful than treatment for AK and simultaneously sun-damaged skin.

Immediately after treatment and on the first day cooling with physiologic saline compresses or e.g. thermal water or thermal water gel, cold cream and/or cool pads is recommended as after-care. On the following days various products for wound and scar care may be employed. The use of topical corticosteroids should be avoided as they inhibit the desired inflammatory reaction in the tissue. Strict sun protection (textile sun protection or products with SPF 50+) is required.

Follow-up should be scheduled on an individual basis. Often within 2–3 days marked swelling or erythema up to

blistering can occur within the context of the phototoxic reaction after PDT. After PDT in the face and on the scalp, small follicular pustules are typically observed; these pustules are sterile, so that no anti-microbial intervention is needed [16]. Prophylactic use of antibiotic or antiseptic preparations is not required. Comprehensive pre-treatment information about these side effects is recommended. The expected aesthetic results based on the new synthesis of collagen in the dermis are observed only after 3–6 months. A return visit for final evaluation of efficacy is therefore sensible after this time [1].

In contrast to PDT for AK, for cosmetic indications a single treatment is not always sufficient; a second or third treatment at intervals of at least 4 weeks is recommended depending on the side effects of PDT. The performance of "maintenance PDT" every 6 months is currently being discussed due to the experiences in the treatment of AK [17]. Seasonal factors do not play a role in planning therapy, as PDT is possible over the entire year; during the summer months and in planned vacations sufficient sun protection must be assured. In the winter the incubation phase should, if possible, be performed in warm rooms or waiting areas, since low outdoor temperatures result in reduced enzymatic conversion of the precursors to PPIX.

Treatment zone: scalp/ hairless area

This treatment region is primarily relevant in men. The same conditions as in PDT of the face are valid. The simultaneous presence of AK must be considered. Occasionally these can be quite keratotic, so that adequate keratolysis must be performed. Presence of already invasive squamous cell carcinomas that can be quite indistinct clinically should be excluded by biopsy, if there is any doubt. It has also been observed that PDT of the scalp is more painful than at other sites of the body so that the possible use of nerve blockade deserves special consideration [15].

Treatment zone: neck and décolleté

On the neck and décolleté fewer sebaceous glands and other skin appendages are found than in the face or on the scalp. Therefore the parameters of possible pre-treatments must be selected carefully, as re-epithelization is poor and requires more time. Also the phase of post-therapeutic erythema is prolonged in this zone [16]. The use of fractional ablative laser systems or microneedling is helpful, while chemical peeling as pre-treatment is possible [18] (Table 1).

The PDT itself does not differ from the technique in the face. About 2 weeks after PDT, topical therapy with the addition of hydroquinone can be considered for those with a tendency for hyperpigmentation.

Treatment zone: back of the hands

In contrast to the neck or décolleté. on the back of the hands pre-treatment can be performed much more aggressively. Particularly in the case of marked keratotic areas the use of keratolytic/ plastic agents (salicylic acid, urea) under occlusion, for example overnight, is sensible. Further pre-treatment measures correspond to other locations. PDT is also performed identically. Frequently healing after PDT on the hand requires more time than in the face; the pain during irradiation in PDT is usually less intense. The products mentioned above can be employed for follow-up treatment.

Repetition frequency of aesthetic PDT

No rules have been established with respect to the frequency of repetition of PDT. There are no limits with respect to repetition; usually 2–3 treatments in 3–6-month intervals are performed until satisfactory results are achieved. The selection of the interval between two PDT sessions depends primarily on the original clinical findings and the individual time needs for healing after the first PDT. In the case of an aesthetic indication, nonetheless, an interval of 4 weeks between individual sessions should be observed, even longer, if indicated, when additional combinations with pre-treatments are made. In case of PDT of epithelial tumors (Bowen's disease, basal cell carcinomas) with MAL, there should be no deviation from the stipulated two-time treatment in an interval of one week. The preparation of an individual therapy plan before the start of therapy is sensible.

Conclusions

While the therapy protocols in the treatment of skin cancers have in the meantime been clearly defined, the treatment parameters in the treatment of signs of skin aging are not yet standardized and vary in part significantly between the different studies. As in actinically damaged skin actinic keratoses or even field cancerization are frequently present, it is recommendable for these patients to always employ therapy protocols licensed for the treatment of AK, in order to guarantee effective treatment of the epithelial skin tumors. Pre-treatment with various systems (microneedling, microdermabrasion, fractional lasers) allow for synergistic effects and can depending on the anatomic treatment zone significantly improve aesthetic results.

Conflict of interest

Prof. Szeimies is a member of the scientific advisory boards of Almirall, Biofrontera, Galderma, Leo Pharma and Spirig,

receives honoraria from these companies for lectures and has participated as trial investigator in numerous licensing studies in the field of dermatooncology. Dr. Lischner is a member of the scientific advisory boards of Almirall, Biofrontera, Spirig and Galderma and receives honoraria from these companies for lectures. Dr. Philipp-Dormston is a member of the scientific advisory boards of Allergan, Biofrontera and Galderma, holds lectures and conducts clinical studies for these companies. PD Dr. Podda is a member of the scientific advisory board of Galderma, receives honoraria for lectures and has participated in studies for Almirall, Galderma and Biofrontera. Dr. Walker, Dr. Hiepe-Wegener, Dr. Feise and Dr. Prager have no conflicts of interest to declare. Dr. Kohl receives honoraria for lectures for Galderma. Prof. Karrer receives honoraria for lectures for Galderma and has participated in licensing studies in the field of dermatooncology as trial investigator.

The organization of the consensus conference of the Working Group Phototdynamic Therapy was supported by Galderma Laboratorium GmbH, Düsseldorf, Germany.

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References

1 Kohl E, Torezan LAR, Landthaler M, Szeimies RM. Aesthetic effects of topical photodynamic therapy. J Eur Acad Dermatol Venereol 2010; 24: 1261–9.
2 Szeimies RM, Torezan L, Niwa A et al. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. Br J Dermatol 2012; 167: 150–9.
3 Dover J, Bhatia AC, Stewart B, Arndt KA. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. Arch Dermatol 2005; 141: 1247–52.
4 Gold M, Bradshaw VL, Boring MM et al. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg 2006; 32: 795–801.
5 Key DJ. Aminolaevulinic acid-pulsed dye laser photodynamic therapy for the treatment of photoaging. Cosmet Dermatol 2005; 18: 31–6.
6 Ruiz-Rodriguez R, Lopez L, Candelas D, Pedraz J. Photorejuvenation using topical 5-methyl aminolevulinate and red light. J Drugs Dermatol 2008; 7: 633–37.
7 Ruiz-Rodriguez R, Lopez L, Candelas D, Zelickson B. Enhanced efficacy photodynamic therapy after fractional resurfacing: fractional photodynamic rejuvenation. J Drugs Dermatol 2007; 6: 818–20.
8 Sanclemente G, Medina L, Villa JF et al. A prospective split-face double-blind randomized placebo-controlled trial to assess the efficacy of methyl aminolevulinate + red-light in patients with facial photodamage. J Eur Acad Dermatol Venereol 2011; 25: 49–58.
9 Karrer S, Kohl E, Feise K et al. Photodynamische Therapie zur Hautverjüngung: Übersicht und publizierte Datenlage – Ergebnisse einer Konsensus-Konferenz des Arbeitskreises Ästhetische Photodynamische Therapie. J Dtsch Dermatol Ges 2013; 11: 137–48.
10 Torezan L, Chaves Y, Niwa A et al. A pilot split-face study comparing conventional MAL-PDT with microneedling-assisted PDT on actinically damaged skin. Dermatol Surg 2013 (in press).
11 Togsverd-Bo K, Haak CS, Thaysen-Petersen D et al. Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: a randomized clinical trial. Br J Dermatol 2012; 166: 1262–9.
12 Forster B, Klein A, Szeimies RM, Maisch T. Penetration enhancement of two topical 5-aminolaevulinic acid formulations for photodynamic therapy by erbium:YAG laser ablation of the stratum corneum: continuous versus fractional ablation. Exp Dermatol 2010; 19: 806–12.
13 Karrer S, Bäumler W, Abels C et al. Long-pulse dye laser for photodynamic therapy: investigations in vitro and in vivo. Lasers Surg Med 1999; 25: 51–9.
14 Babilas P, Knobler R, Hummel S et al. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. Br J Dermatol 2007; 157: 111–7.
15 Halldin CB, Paoli J, Sandberg C et al. 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.
16 Lehmann P. Nebenwirkungen der topischen photodynamischen Therapie. Hautarzt 2007; 58: 597–603.
17 Apalla Z, Sotiriou E, Chovarda E et al. Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. Br J Dermatol 2010; 162: 171–5.
18 Peterson JD, Goldman MP. Rejuvenation of the aging chest: a review and our experience. Dermatol Surg 2011; 37: 555–71.

