

Photodynamic Therapy: A Clinical Consensus Guide

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BACKGROUND The American Society of Dermatologic Surgery (ASDS) periodically develops consensus documents for its members concerning various aspects of dermatologic surgery. Advances in photodynamic therapy (PDT) have been many and PDT use has been established in a variety of skin conditions.

OBJECTIVE The ASDS board of directors proposed a committee of experts in the field to develop consensus documents on different treatments. An expert panel reviewed the literature on PDT and discussed the findings. The consensus was reached with evidence-based recommendations on different clinical applications for PDT.

PATIENTS AND METHODS This consensus document includes discussions regarding PDT, including different photosensitizers and various light source activators, historical perspective, mechanism of action, various therapeutic indications and expected outcomes, pre- and post-care, and management of adverse outcomes.

RESULTS Photodynamic therapy is highly effective for pre-cancerous lesions, superficial nonmelanoma skin cancers, inflammatory acne vulgaris and other conditions. New protocols including laser mediated PDT significantly improve results for several indications.

CONCLUSION The ASDS consensus document on PDT will be helpful for educating members on safe and effective PDT for a variety of indications.

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Photodynamic therapy (PDT) relies on the interaction between a photosensitizer, the appropriate activating wavelength of light, and oxygen. The reaction generates reactive oxygen species (ROS) in cells that either take up an exogenous photosensitizer or produce its own endogenously, causing cell death by necrosis or apoptosis, but minimally affects the surrounding tissue. Initially, PDT relied on systemic administration of the photosensitizer, but the advent of topical application revolutionized the field. The main types of topical photosensitizer prodrugs used for PDT are 5-aminolevulinic acid (5-ALA) or its derivatives.

The main derivative used is methyl aminolevulinate (MAL) which is demethylated by the target tissue to produce ALA. Exogenously applied ALA and MAL bypass the intracellular rate-limiting step in the heme synthesis pathway to produce the actual photosensitizers, protoporphyrin IX, and other porphyrins. Over the past 100 years, PDT has evolved into a safe and effective dermatologic treatment option for actinic keratosis/cheilitis, superficial nonmelanoma skin cancer (NMSC), and more recently, photoaging, acne, rosacea, sebaceous hyperplasia, and verrucae.¹⁻⁴ Topical PDT offers the advantage, when

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compared with other destructive modalities, of being able to selectively and effectively target and simultaneously treat lesions over large surface areas with little or no risk of scarring. Furthermore, PDT has also expanded outside of the field of dermatology and is now used as adjuvant therapy to treat pulmonary, respiratory tract, neural, and urinary tract tumors, and vitreoretinal disease.

Historical Perspective

Ancient civilizations have known for thousands of years that they could combine different plants with sunlight to treat various skin diseases. It was not until about 100 years ago that Hermann von Tappeiner coined the term “photodynamic action” to describe an oxygen-dependent reaction following photosensitization.⁴ He noted that in the absence of oxygen, dye and light alone did not cause cell death. He continued to develop the concept of PDT and eventually described the first cases in humans, using eosin as the photosensitizer to treat various skin conditions, including condyloma lata and NMSC. Over the years, many photosensitizers have been used, and the most studied agent was hematoporphyrin. However, hematoporphyrin had to be administered intravenously and was cleared from tissue very slowly, resulting in prolonged phototoxicity.

In 1990, Kennedy reported the use of 5-ALA and visible light for topical PDT treatment of the skin. ALA was revolutionary because it easily penetrated, damaged or abnormal stratum corneum and rapidly cleared. Using a single application to treat basal cell carcinoma (BCC), Kennedy and colleagues⁵ were able to achieve a 90% complete response rate.

Basic Principles of Photodynamic Therapy

Photodynamic therapy is the interaction among 3 ingredients: light, a photosensitizer, and oxygen (Figure 1). After exposure of the photosensitizer to light containing its action spectrum, ROS, especially singlet oxygen radicals, are generated. The ROS affect all intracellular components, including proteins and DNA, resulting in necrosis or apoptosis.⁶ The accumulation of the photosensitizer within cells, where it is preferentially produced or taken up, results in tissue destruction while minimizing surrounding tissue damage, often resulting in an outstanding cosmetic result.

Photosensitizers

5-aminolevulinic acid has revolutionized the field of PDT. It has a low molecular weight that allows it to easily penetrate the stratum corneum. Maximum

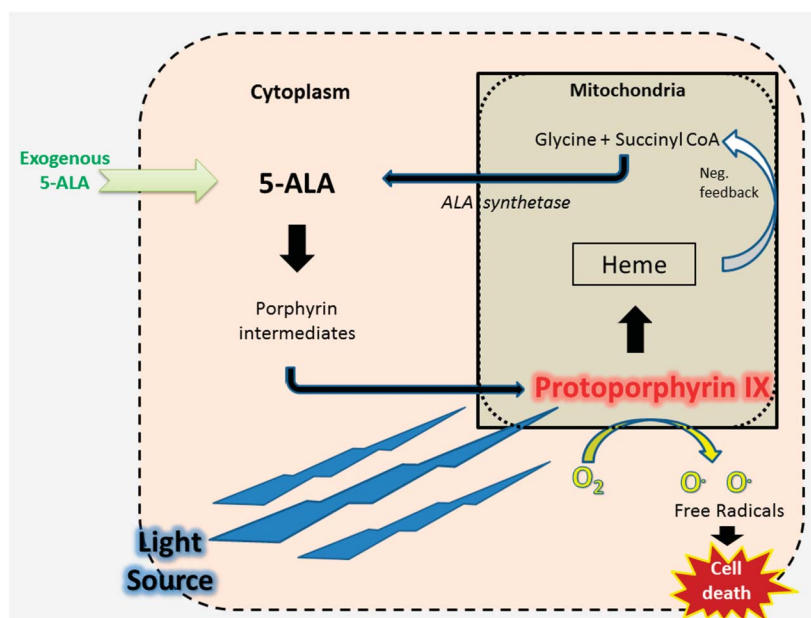


Figure 1. Mechanism of PDT. Exogenous aminolevulinic acid (ALA) enters the porphyrin-heme pathway and is converted endogenously into the PpIX. Once PpIX is activated by the proper wavelength of light, it produces singlet oxygen free radicals, which destroy the target cell (courtesy of Ali M. Rkein, MD).

concentration of photosensitizer protoporphyrin IX (PpIX) has been shown to occur about 6 hours after the end of the 4-hour incubation of ALA 20%^{7,8} and is cleared from the skin within 24 to 50 hours of application.⁹ ALA is the first compound synthesized in the porphyrin–heme pathway and is converted endogenously into the PpIX. Once PpIX is exposed to its visible light action spectra (including PpIX absorption peaks at 400–410 nm and 635 nm), ROS are generated, which destroy the target cell. Although the heme synthesis pathway is controlled by ALA synthase, exogenous ALA bypasses this rate-limiting enzyme and overwhelms the cell's ability to convert PpIX into heme. ALA is thought to preferentially target tumors of epithelial origin because of their defective epidermal barrier and slower conversion of PpIX into heme. In the United States, ALA is available as a 20% solution and is marketed under the trade name Levulan (DUSA Pharmaceuticals, Inc., Wilmington, MA). It is FDA approved since 1999 and approved for the treatment of nonhyperkeratotic actinic keratosis (AKs) on the face and scalp in conjunction with a blue light source.¹⁰ It is supplied as a cardboard tube housing 2-sealed glass ampules, one containing 354 mg of δ -ALA hydrochloride powder and the other 1.5 mL of solvent.⁶ These separate components are mixed within the cardboard sleeve just before use.

An alternative to ALA is the methyl ester form, MAL.⁶ The presence of methyl ester group makes the molecule

more lipophilic and enhances penetration; however, MAL must be demethylated back to ALA by intracellular enzymes. Although this may limit the availability of ALA, MAL has been shown to reach maximal intracellular concentrations of PpIX quickly, allowing a shorter incubation period. In the United States, MAL was available for a brief period of time as a 16.8% cream and marketed under the trade name Metvixia (Galderma Laboratories, L.P., Ft. Worth, TX). However, it is currently unavailable in the US market, but remains widely used in Europe.

Light Source

Several light sources, including coherent and incoherent light, have been used in PDT. PpIX has a strong absorption peak between 405 and 415 nm (Soret band), along with several smaller Q bands from 500 to 630 nm; the last peak is at 635 nm (Figure 2). Blue light, which includes the wavelength of 405 nm, efficiently excites PpIX and is commonly used. The most widely available fluorescent lamp light source is the Blu-U (DUSA) with a peak emittance at 417 ± 5 nm.¹¹ Because of its relatively short wavelength, blue light penetrates about 2 mm, whereas red light (635 nm) is used for thicker lesions because it has a greater than 2-mm penetration.¹² The 635-nm wavelength targets the last Q band; because red light does not excite PpIX as efficiently as blue light, a higher fluence (dose) is needed.⁷ However, the consensus group noted that

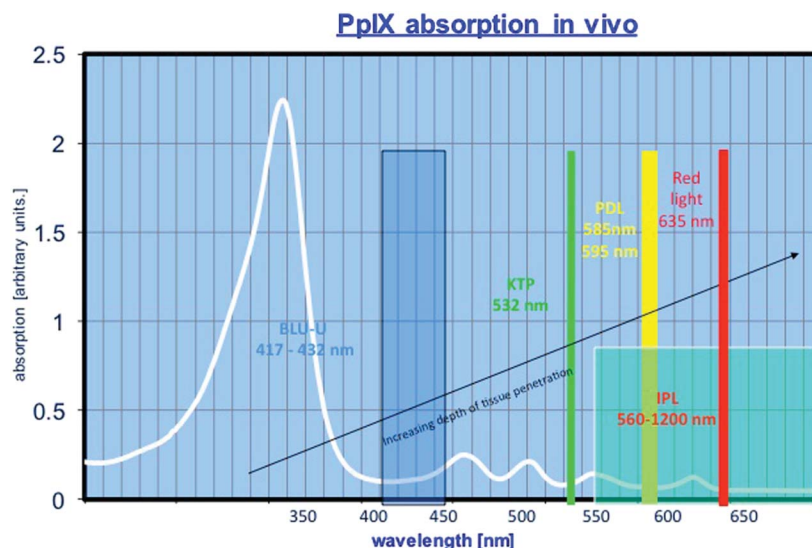


Figure 2. Absorption spectrum of PpIX in the ultraviolet and visible spectrum (courtesy of David M. Ozog, MD).

clinically blue light is effective in some instances where you would only expect red light to work. This may be related to incomplete knowledge as to the number of photons needed to activate aminolevulinic acid. The reported penetration depths for various wavelengths of light reflect the point at which 50% of the photons have penetrated and the depth of an activity of the remaining photons is unclear with either red or blue light. For instance, a 488-nm argon ion laser has 200 μm of tissue penetration compared with a 694-nm ruby laser which has a 1200- μm penetration depth of 50% of the photons in white skin.¹³

Intense pulsed light (IPL) is a source of incoherent light, which emits a radiation spectrum from approximately 500 to 1,200 nm.⁸ Cutoff filters allow customization of the delivered wavelengths. This light source is particularly useful in photorejuvenation, targeting pigment, blood vessels, and even collagen. Light-emitting diodes (LEDs) provide a narrower spectrum of light irradiation, usually in a 20- to 50-nm bandwidth through a compact, solid, but powerful semiconductor.⁸ Light-emitting diodes are simple to operate and are typically small in size, emitting light from the UV to IR portion of the electromagnetic spectrum. However, the diminutive size of most commercially available LED panels necessitates multiple rounds of light illumination to treat larger areas. Daylight PDT is being increasingly researched and used, particularly in Europe.¹⁴ Combined with minimal incubation time, daylight PDT produces results with little to no discomfort to patients. In addition, no equipment is needed and patient time in clinicians' office is minimized. Challenges include determining and standardizing exposure times for various latitudes and seasonal light variances.

Lasers provide precise doses of light radiation. As a collimated light source, lasers deliver energy to target tissues at specific wavelengths chosen to mimic absorption peaks along the porphyrin curve. Lasers used in PDT include the tunable argon dye laser (blue-green light, 450–530 nm),¹⁵ the copper vapor laser-pumped dye laser (510–578 nm), long-pulse pulsed dye lasers (585–595 nm), the Nd:YAG KTP dye laser (532 nm), the gold vapor laser (628 nm), and solid-state diode lasers (630 nm).^{16,17} Fractionated

ablative lasers, although not “light sources,” are increasingly used to pretreat lesions, enhancing penetration and efficacy across multiple indications. The impressive early data are discussed in each clinical subsection throughout this article.

It is important to consider the fluence (J/cm^2) and irradiance (mW/cm^2) that are used in PDT. The effective photobleaching dose for a light source of approximately 405 nm is 10 J/cm^2 , and a 10-fold increase, or 100 J/cm^2 for a light source of 635 nm. This is why a typical PDT treatment with blue light would take less time than a treatment with red light if the fluences were identical. Red light requires a longer irradiation period because it does not excite PpIX as efficiently as blue light. However, many red light devices in use have a higher fluence compared with blue light devices and thus the time to treat can be quite similar. In addition, because PDT consumes oxygen, it is important to use an appropriate rate of fluence (i.e., irradiance) as a high irradiance may consume the oxygen molecules too quickly, leading to a decrease in efficiency.⁶ Some researchers believe that this significantly decreases the clinical effect when using lasers for PDT treatment. Thus, the fluence should be kept in the range of 150 to 200 mW/cm^2 to avoid hypoxic effects on tissue.^{18,19} In fact, there is evidence to support that cumulative light doses of greater than 40 J/cm^2 can deplete all available oxygen sources during the oxidation reaction, making higher doses of energy during PDT unnecessary.²⁰

Preoperative Care

After medical or cosmetic indications for PDT have been ascertained, focus should be turned to peri-procedural details. It is imperative to obtain a proper patient medical history. Any history of photosensitizing disorders, porphyrias, or documented allergy to ALA or MAL may preclude treatment.^{21–24} Because only visible light is used for activation, concurrent use of medications known to cause toxicity with exposure to UV light is allowed and should not be an issue. Previous history of herpes simplex virus (HSV) should be elicited and some authors initiate prophylactic measures taken before the initiation of therapy.²⁵ However, members of this consensus

group do not routinely give prophylactic therapy to patients with HSV history. Skin conditions, which promote parakeratotic scale, such as seborrheic dermatitis, should be treated and controlled before PDT, as this type of scale is more hyperproliferative and can absorb ALA.

Many methods exist for pretreatment preparation of skin-cleansing regimens. Cleaning allows for a more uniform penetration of the ALA and subsequent photoactivation. Acetone is frequently used to degrease the skin and facilitate penetration, however, it has a low flash point, can be painful for open or eroded skin, and its availability may be limited at larger academic institutions. Thus, other cleaning agents are sometimes used. Peikert and colleagues²⁶ showed equal degreasing capability between acetone and hibiclen for prepping skin before chemical peeling. Isopropyl alcohol, soaps, alpha-hydroxy/salicylic acid cleansers, or towelettes can also be used.

After cleansing, numerous techniques (ranging from noninvasive to minimally invasive) can be used to disrupt the stratum corneum and enhance the skin penetration of ALA. The trade-off of these methods is added time and expense of supplies as well as staffing. One simple method is gauze abrasion or the heavy-handed use of 4×4 gauze rubbed on the skin. Oscillating brushes or particle/particle-free microdermabrasion has also been reported as methods of enhancement of penetration.²⁷ The use of micro-needling rollers has been studied and shown to promote ALA penetration, absorption, and activation.²⁸ More recently, fractional nonablative and ablative fractional lasers have been used before application to enhance penetration, activation, and efficacy^{29–32} This use of fractional lasers to enhance delivery will be thoroughly discussed by indication throughout this article.

The application of the topical ALA solution (after mixing per package insert) should be carefully considered. Ideally, the use of the Kerastick (DUSA Pharmaceuticals) cotton-tipped applicator facilitates placement. Application to the full face is best accomplished expressing the solution onto the treatment area and with a gloved hand evenly wiping it over the face in 2 coats. Care should be taken to apply within close

proximity to avoid dripping solution. Because actinic damage is frequently present in the lateral/medial brows and into the frontal and sideburn hairlines, these areas should not be overlooked. For nonfacial areas, such as the extremities, occlusion has been used to increase penetration. This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied. Applying a warming blanket can also enhance penetration and increase clearance of actinic keratosis as demonstrated in a prospective clinical trial.³³

Incubation times will vary and depend on the type of treatment (cosmetic vs medical), anatomical area treated, the severity of the actinic damage, and patient tolerance. For the treatment of actinic damage on the face, incubation times of 1 to 2 hours are commonly used in clinical practice.^{14,34} This reduction in treatment time was done primarily for patient and physician convenience as the initial studies had incubation times of 14 to 18 hours which maximized PpIX levels in actinic tissue. On the scalp, typically a minimum of 2 hours is used for incubation. A recent multicenter randomized study found the median AK clearance rate at 12 weeks to be 88.7% for extremities, when treated with ALA under occlusion for 3 hours and irradiated with blue light (10 J/cm^2).³⁵ These shorter incubation times have resulted in reduced, but acceptable, clearance rates of actinic keratosis compared with initial FDA trial data. Incubation should take place in a dark room, devoid of as much ambient light as possible. Typically, discomfort during light treatment will increase with longer incubation times as additional drug is converted to active form. For this reason as well as cost and patient convenience, many European centers have been conducting “daylight” PDT, where patients incubate for a much shorter period before spending a few hours outdoors for exposure rather than a device in the clinician’s office.³⁶ Sunscreen is used during this time to prevent UV-induced sunburn because it does not interfere with the visible light activation of PpIX (unless it is applied thickly in an opaque manner). Appropriate exposure times have been developed for various latitudes and weather conditions.

After incubation, the targeted area may be gently washed with water and a cleanser. Irradiation should

be performed in an appropriately sized room preferably without windows and with low ambient light levels (to prevent phototoxicity or photobleaching). The room should also have adequate cooling and ventilation for the light source.

Appropriate eye protection is paramount during all aspects of the procedure to ensure ocular safety. Prolonged exposure to blue and ultraviolet light is damaging to the retina and increases the risk of cataracts.³⁷ Red light does not seem to result in the same retinal toxicity, but ocular protection is still recommended. In the pivotal Phase III FDA trial for actinic keratosis, the fluorescent lamp light source was the Blu-U (DUSA) with a peak emittance at 417 ± 5 nm, and blue-blocking goggles were worn by patients during irradiation.³⁸ Because a wider variety of light sources are used nowadays, the type of goggles used must be suitable to the light source. The preference is for patients to use completely opaque eye protection to minimize exposure. All staff or providers should wear appropriate eyewear before entering the room.

Therapeutic Applications and Expected Outcomes

Since the advent of PDT, the list of indications has continued to grow. The following sections will focus on the treatment and expected outcomes of actinic keratosis, NMSC, acne, photorejuvenation, and verrucae. Please see Tables 1–4 which outline therapeutic applications and expected outcomes of PDT, a general PDT protocol, home care instructions, and typical settings used in PDT, respectively.

Actinic Keratosis

In the United States, the only FDA-approved indication (1999) for PDT is the treatment of non-hyperkeratotic AKs on the face and scalp in conjunction with a blue light source.⁶ The initial FDA Phase II and III studies of ALA-PDT (Levulan Kerastick; DUSA) in the treatment of non-hyperkeratotic actinic keratosis on the face and scalp had a clearance rate of 85% to 90% after 1 to 2 treatment sessions. The ALA was applied for 14 to

TABLE 1. Indications and Expected Outcomes

Indications	Summary of Recommendations
Actinic keratosis	Highly effective When treating head and neck, efficacy similar to, or exceeds other FDA-approved modalities Better cosmetic outcome when compared with cryotherapy
Squamous cell in situ (Bowen disease)	Efficacy likely superior to cryotherapy and 5-FU Good cosmetic outcome Clearance rates are between 80% and 82% at 1 yr
Actinic cheilitis	Conventional PDT is not very effective with clearance rates that range from 29% to 47%. However, with laser-assisted PDT, the clearance rates jump to 85%.
SCC prevention in solid organ transplants	Cyclic PDT at intervals of 1–2 months can reduce the occurrence of new lesions by 79% and 95% at years 1 and 2, respectively.
Superficial BCC	Highly effective and similar to simple excisions Very useful in treating multiple lesions Main disadvantage is time commitment
Nodular BCC	May be used in specific patients when other options are not appropriate
Acne vulgaris	Highly effective in the treatment of inflammatory papules, but not comedones Excellent option for moderate-to-severe acne when isotretinoin is not an option Drawbacks include time commitment, discomfort during treatment, posttreatment erythema, and crusting
Photorejuvenation	Pulsed dye laser (PDL) as a light source can also help with early erythematous scars Excellent cosmetic results for all facets of photodamage Multiple other proven and accepted modalities, which are less expensive and require less time
Verrucae	Very effective, but rarely used by the authors Reported clearance rates of hand and foot warts ranging from 56% to 100% Reported clearance rates of condyloma acuminata ranging from 66% to 79%

TABLE 2. Photodynamic Therapy General Treatment Protocol

Patient washes the area to be treated with soap and water
Acetone- or alcohol-soaked 4 × 4 gauze is used to remove any remaining debris and oil
The photosensitizer is evenly applied to the entire area to be treated. A second coat of the photosensitizer can be applied, after the first coat has dried.
Allow the photosensitizer to incubate for 0.5–4 hours (see below for more comprehensive recommendations)
Activate the photosensitizer with the appropriate light source
Patient to wash the treated area with soap and water to remove any residual photosensitizer
The patient must stay out of the any direct sunlight for 48 h
Repeat as needed in 2–3 wk

18 hours, followed by irradiation with a blue light source (10 J/cm²) for 1,000 seconds. Since then, different protocols have been developed to improve the efficacy for other indications and to reduce the discomfort and time associated with the administration of PDT.⁶ The byproduct of these reduced incubation time protocols is a reduction in the clearance rates seen in the initial FDA Phase II and III studies in most subsequent clinical trials. In a European multicenter, randomized, prospective study with 119 subjects and 1,500 lesions, MAL-PDT was compared with cryosurgery in the treatment of actinic keratosis. Patients were randomized to either a single treatment with MAL-PDT (3 hours of incubation with illumination with broad-spectrum red light; 75 J/cm²) or a double freeze–thaw cycle of liquid nitrogen. They found no

significant difference between the 2 treatment modalities, but MAL-PDT provided a superior cosmetic result.⁴⁰ Pariser and colleagues,⁴¹ in a multicenter, randomized, double-blind study treating AKs with MAL-PDT, found a clearance rate of 67% after the initial treatment and 90% after retreatment. Touma and colleagues³⁴ examined the effect of pretreatment with urea (to enhance ALA penetration) and concluded that urea did not influence the therapeutic outcome. Finally, a recent Cochrane review found that ALA-PDT or MAL-PDT, with blue or red light, resulted in similar efficacy in the treatment of actinic keratosis; however, for ALA-PDT, longer incubation (4 hours) resulted in better results compared with shorter incubation time (<2 hours).⁴² The review also found that 4-hour incubation with ALA-PDT was

TABLE 3. Sample Home Care Instructions for Patients Following Photodynamic Therapy**Day of Treatment**

1. Remain indoors and avoid direct sunlight for 36 hours. VERY IMPORTANT!!! Do not sit by a window.
2. Spray on Avene Thermal Spring Water often.³⁹
3. Wash the face twice a day with a gentle cleanser.
4. Apply bland moisturizing cream 4 times a day.
5. Take analgesics such as ibuprofen if there is any pain.
6. If you have any discomfort, apply ice packs to the treated area for 5–10 minutes every few hours. This will help keep the area cool and alleviate any discomfort, as well as help keep down any swelling. Swelling will be most evident around the eyes and is usually more prominent in the morning.
7. Redness of the face may be very intense for the first day or 2.

Day 2–7:

1. Wash the face twice a day with a gentle cleanser
2. The skin will feel dry and tightened; a bland moisturizing cream should be used twice a day.
3. You may begin applying make-up once crusting has healed. The area may be red for 3–5 days. If make-up is important to you, please use mineral make-up, which is all natural, inert, and small anti-inflammatory and acts as a concealer with sunscreen. It is especially effective to mask redness.
4. When outdoors, use a “physical block” sunscreen with zinc oxide or titanium dioxide and a minimum SPF 30. Consult with your skin care professional for a sunscreen recommendation.

If you have any questions or concerns, please do not hesitate in contacting our office.

TABLE 4. Photodynamic Therapy Specific Treatment Protocols for Different Indications

<i>Indication</i>	<i>Topical Photosensitizer</i>	<i>Incubation Period</i>	<i>Light Source</i>	<i>Dose</i>	<i>Comments</i>
Actinic keratosis	ALA	1–4 h	Blue light	10 J/cm ²	Requires 1–2 sessions of PDT for optimal results
		1–4 h	Red light	75–150 J/cm ²	Sunscreen necessary for daylight PDT
Bowen disease	MAL	0.5 h	Daylight	2 h	Requires 2–3 sessions of PDT for optimal results
	ALA	1–3 h	Red light	37–75 J/cm ²	
Superficial BCC	MAL	4 h	Red light	≥100 J/cm ²	Requires 2–3 sessions of PDT for optimal results
	ALA	3 h	Red light	75–100 J/cm ²	
Acne vulgaris	MAL	3–6 h	Red light	≥60 J/cm ²	Requires 2–3 sessions of PDT for optimal results
	ALA	3 h	Red light	37–75 J/cm ²	
Photorejuvenation	ALA	3 h	Blue light	10 J/cm ²	2–3 treatments, repeated biweekly
	ALA	3 h	Red light	37 J/cm ²	
	MAL	3 h	Red light	37 J/cm ²	
	ALA	30 min–3 h	Blue light	10 J/cm ²	
	ALA	30 min–3 h	Red light	37 J/cm ²	2–3 treatments, repeated monthly
	MAL	30 min–1 h	Red light	37 J/cm ²	

ALA, aminolevulinic acid; BCC, basal cell carcinoma; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

significantly more efficacious than cryotherapy, but 1-hour incubation with ALA-PDT (blue light or pulsed dye laser) was not significantly different than 0.5% 5-fluorouracil (5-FU). Lastly, the review found that MAL-PDT had similar efficacy regardless of the light source used (red light, broadband visible light with water-filtered infrared A, and daylight).

In an attempt to increase AK clearance from a single PDT treatment, 2 of the authors (M.P.G. and S.G.F) showed that multiple sequential laser and light sources (IPL, PDL, blue light, and red light) led to significantly greater AK clearance than that achieved with a single light source (blue light), without significant differences in posttreatment adverse events.¹⁷ They hypothesized that the sequential use of different light sources affects multiple absorption peaks of PpIX, perhaps similarly to daylight PDT which activates PpIX at multiple wavelengths.^{43,44}

Several studies to increase the efficacy of PDT through the use of fractional surface ablation to increase the penetration of ALA through the stratum corneum have been performed. Each study shows superiority with ablative fractional laser pre-

treatment. Ko and colleagues treated 40 patients with 236 facial AKs in a prospective randomized nonblinded trial. All the patients were treated with MAL-PDT, but 23 of the patients with 135 AKs were pretreated with 2,940-nm ablative fractional Erbium:yttrium-aluminum-garnet (Er:YAG) laser (ablation depth of 300–550 μ m, 22% treatment density and a single pulse).⁴⁵ The patients were followed up for 1 year. They found that the pretreatment with the fractional Er:YAG laser was significantly more effective in treating AKs of all grades (86.9% vs 61.2%), but was even more pronounced in thick hyperkeratotic lesions (69.4% vs 32.5%). They also noted a much lower recurrence rate in the laser group compared with the traditional MAL-PDT group (9.7% vs 26.6%). More erythema and hyperpigmentation were seen in the laser group, but were mild and well tolerated. In addition, Choi and colleagues treated 93 patients with facial and scalp AKs and randomized to traditional MAL-PDT with 3 hours of incubation, or Er:YAG ablative fractional laser-assisted MAL-PDT (AFL-PDT) with 2 or 3 hours of MAL incubation. Patients were followed at 3 and 12 months. At 3 months, they noted that the 3-hour AFL-PDT was significantly

more efficacious in the treatment of AKs when compared with 2-hour AFL-PDT and traditional 3-hour MAL-PDT, 91.7%, 76.8%, and 65.6%, respectively. This trend remained true at 12 months. Thus, they recommended 3-hour AFL-PDT over short-incubation AFL-PDT and traditional MAL-PDT.⁴⁶ Togsverd-Bo and colleagues⁴⁷ combined fractional Er:YAG with daylight PDT in transplant patients for treatment of AKs. Sixteen patients with 542 AKs in field-cancerized skin of the scalp, chest, and extremities were treated. Complete response rates in areas pretreated with fractional Er:YAG followed by daylight PDT had the highest efficacy at 74% 3 months after treatment compared with conventional PDT without laser and laser alone. The density of the fractional laser was remarkably low at 2% to 4% and pain averaged 0/10 for this arm of the study. Authors concluded that this protocol is quite tolerable and may be preferable for treatment of difficult AKs in organ transplant patients.

Actinic Cheilitis

Actinic cheilitis is a premalignant condition localized to the lips, which can progress to invasive squamous cell carcinoma (SCC), similar to AKs on the skin. In 2015, Yazdani Abyaneh and colleagues⁴⁸ completed a systemic review that examined the treatment of actinic cheilitis with PDT. They examined 15 case series that included 242 patients. Both ALA and MAL were used, with incubation periods that ranged from 2 to 4 hours. Red light (630 nm) irradiation was used for both ALA and MAL; range 37 to 80 J/cm². When they examined the studies that evaluated for complete clinical response, they found the rate to be 62% with a follow-up period ranging from 3 to 30 months. The studies that examined histological clearance found a cure rate of 47% with a follow-up period ranging from 1.5 to 18 months. The most common reported adverse events reported were pain and burning, which resolved within 2 weeks. They also reported good to excellent cosmetic results in most patients. This result is lower than reported cure rates of up to 96% to 99% with surgical excision; however, excision can be associated with a marked increase in morbidity, including scarring.⁴⁹

Choi and colleagues²⁹ examined the efficacy of ablative fractional laser-assisted PDT of actinic cheilitis. They enrolled 33 patients with actinic cheilitis, to either pretreatment with Er:YAG (300 μ m ablation depth, 22% treatment density, and a single pulse) followed by MAL-PDT or 2 sessions of MAL-PDT, 1 week apart. Methyl aminolevulinate was applied under occlusion for 3 hours, followed by red light irradiation (636 nm, 37 J/cm²). Patients were followed up to 1 year with biopsies performed at 3 months and 12 months. They found that pretreatment with Er:YAG laser followed by MAL-PDT was significantly more effective in producing complete response than 2 sessions of MAL-PDT, 85% versus 29%, respectively. At 12 months, the recurrence rate was also significantly lower in the laser Er:YAG group versus the MAL-PDT group, 8% versus 50%, respectively. The 2 groups had similar cosmetic and safety outcomes. They noted good to excellent cosmetic results in 73% and 60% of the Er:YAG and MAL-PDT groups, respectively. All patients experienced local adverse reactions including erythema, burning, and swelling which resolved within 1 week. They concluded that pretreatment with the Er:YAG laser had significant benefits to patients in the treatment of actinic cheilitis.

Alexiades-Armenakas and Geronemus⁵⁰ reported in 2004 using laser-mediated PDT for actinic cheilitis. They treated 19 patients with a 595-nm pulsed dye laser (7.5 J/cm², 10-mm spot, and 10-ms pulse duration). One to 3 treatments were given in 1-month intervals. The complete response rate was 13/19 or 68% after a mean of 1.8 treatments. For several years, 1 author (D.M.O.) has had success using the 595-nm pulsed dye laser as an adjuvant to PDT (immediately after) with red light for treatment of actinic cheilitis. A 10 $\times$ 3 mm spot size is used with a 1.5-ms pulse duration and 7.5 J/cm². Five to 7 passes are performed over the affected area (typically near the lower vermillion border). Efficacy is improved versus red light PDT alone but inferior to reported fractional Er:YAG PDT results (unpublished data).

In summary, treatment of actinic keratosis on the face and scalp with PDT (Figure 3) and actinic cheilitis of

the lip have expected outcomes which are equal to, or exceed other FDA-approved treatment modalities. Fractional ablative laser pretreatment improves outcomes in all published studies. Many patients who have previously undergone treatment with cryotherapy, topical 5-FU, or imiquimod ultimately prefer PDT. This may be due to decreased peak pain compared with cryotherapy, shorter total treatment and recovery time compared with many topical agents, and/or improved cosmetic outcomes. Tierney and colleagues⁵¹ assessed patient perceptions and preferences in the management of actinic keratosis and found that PDT had faster recovery and improved cosmetic outcome when compared with surgical excision and cryotherapy. Furthermore, patients preferred PDT to 5-FU or imiquimod.

For actinic keratosis on the trunk and extremities, there is a marked decrease in clinical efficacy with PDT (Figure 4). Measures such as increased incubation time, curetting of lesions before the administration of PDT, occlusion, fractional ablation, sequential laser and light sources, warming, and/or pretreatment with topical agents are used to improve outcomes in these areas.

Nonmelanoma Skin Cancer

Squamous Cell Carcinoma In Situ (Bowen Disease). Multiple studies have demonstrated that PDT is effective in treating Bowen disease. Bowen disease is defined as full-thickness epidermal atypia without invasion into the dermal layer. Morton and colleagues⁵² conducted several clinical trials to optimize ALA-PDT for the treatment of Bowen

disease. The authors concluded that red light (630 nm) was superior to green light (540 nm) in both complete clearance and recurrence rates. They also conducted a placebo-controlled, randomized, multicenter study that compared the efficacy of MAL-PDT with cryotherapy and 5-FU in the treatment of Bowen disease. Methyl aminolevulinate was incubated for 3 hours followed by irradiation with a broadband red light (75 J/cm², 570–670 nm). Treatment was repeated 1 week later. At 3 months, repeat treatment was performed on lesions with a partial response. At 1 year, the estimated sustained lesion complete response rate of MAL-PDT was superior to cryotherapy (80% vs 67%) and 5-FU (80% vs 69%). Furthermore, Salim and colleagues⁵³ compared ALA-PDT with topical 5-FU in the treatment of Bowen disease. ALA was incubated for 4 hours followed by irradiation with narrow-band red light (630 nm, 100 J/cm²). Both ALA-PDT and 5-FU were repeated 6 weeks later as necessary. One year later, they found that 82% of the lesions treated with PDT showed complete response versus 42% with 5-FU.

Ko and colleagues examined the effect of pretreatment with fractional Er:YAG laser in the treatment of Bowen disease on the lower extremities.²³ Twenty-one patients with 58 Bowen disease lesions were either pretreated with Er:YAG laser (550–600 μ m ablation depth, Level 1 coagulation, 22% treatment density and a single pulse) followed by MAL-PDT or 2 sessions of MAL-PDT (3 hours of incubation followed by red-light illumination 37 J/cm²). At 3 months, they found that pretreatment with the Er:YAG laser followed by MAL-PDT was significantly more effective

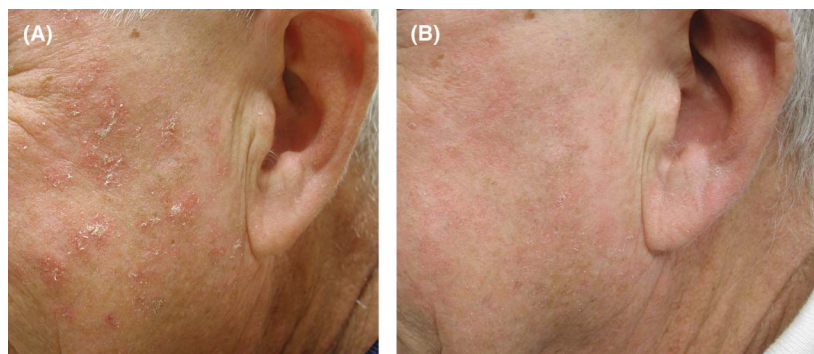


Figure 3. Actinic keratosis on the left cheek (A) before and (B) after treatment with PDT using 20% aminolevulinic acid and blue light (courtesy of David M. Ozog, MD).

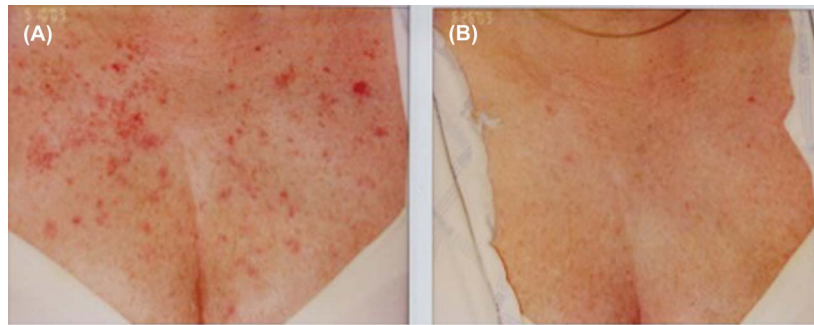


Figure 4. Photodamage and actinic keratosis on the chest, before (A) and 16 days after (B) 10% 5-ALA (1 hour of incubation) (courtesy of Nicholas J. Lowe, MD).

than the 2 treatments of MAL-PDT, 93.8% versus 73.1%. They also found that the recurrence rate was also significantly lower in the Er:YAG laser, 6.7% versus 31.6%, 1 year later. They concluded that the pretreatment with the Er:YAG laser followed by MAL-PDT was significantly more efficacious and had a lower recurrence rate when compared with 2 treatments of MAL-PDT.

Although PDT has demonstrated promising results in the treatment of Bowen disease, the same is not true for invasive SCC. Lansbury and colleagues⁵⁴ examined 118 studies to assess 7 interventions in the treatment of nonmetastatic cutaneous SCC. They found the pooled average recurrence rate for SCCs treated with PDT to be 26.4%, which was much higher than the average local recurrence rate of 5.4% after standard surgical excision. This was the highest recurrence rate when compared with the other modalities, including cryotherapy (0.8%), curettage and electrodesiccation (1.7%), Mohs (3.0%), and radiation (6.4%). Of note,

the lesions treated with cryotherapy and curettage and electrodesiccation were small low-risk lesions. Therefore, clinicians will want to be confident that invasive SCC does not exist within the in situ lesion before treating with PDT. Lesions that we would caution against treating with PDT include those over 2 cm, polymorphic lesions where biopsy may not represent true histologic sample, and any lesions with dermoscopic characteristics of invasive SCC.

In clinical practice, clearance rates for typical Bowen disease are acceptable and average 80% to 82% when treated with PDT, which may be superior to 5-FU at 1 year posttreatment (Figures 5 and 6). Recurrent lesions can either be treated again with PDT, or surgically treated by excision, electrodesiccation/curettage, or Mohs surgery depending on size and location. Large areas of field cancerization can be treated and nonresponsive areas biopsied for invasive disease and/or treated with other modalities. In the United States, PDT may have significantly lower out of



Figure 5. (A) Right hand with multiple Bowen disease and (B) after 2 sessions of PDT using 20% aminolevulinic acid and blue light combined with pulsed-dye laser. Of note, the residual lesion on the fifth digit was treated with Mohs surgery (courtesy of David M. Ozog, MD).

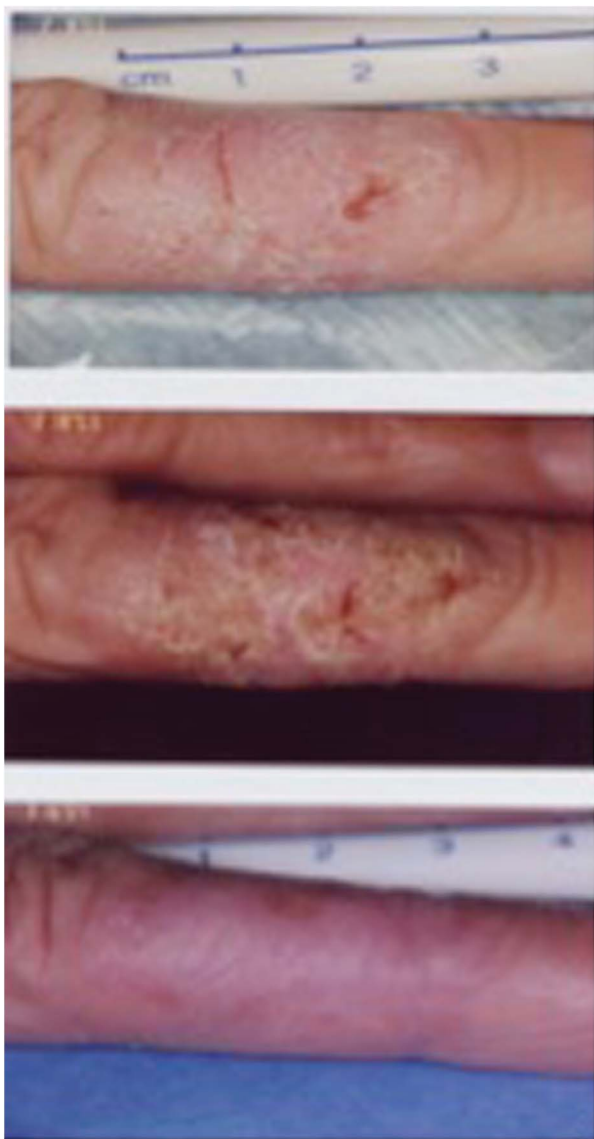


Figure 6. Bowen disease of a finger before MAL-PDT (top), after 1 treatment (middle), and after 3 treatments (bottom) and remains in remission, 11 years post-PDT (courtesy of Nicholas J. Lowe, MD).

pocket costs for patients without prescription coverage, or with a high prescription deductible.

Squamous Cell Carcinoma Prevention in Solid Organ Transplants

Solid organ transplant recipients (OTRs) are at an increased risk of NMSC, especially SCC which is associated with increased morbidity and mortality. Willey and colleagues⁵⁵ treated 12 high-risk solid organ transplant patients with cyclic ALA-PDT (1 hour of incubation, 1,000 seconds at 10 mW/cm²

of 417-nm blue light) at 4- to 8-week intervals for 2 years. They compared the rate of new SCCs found 1 and 2 years post-cyclic PDT to the patients rate the 1 year before the initiation of the cyclic PDT. They found the median reduction in the rate of new SCCs at the 1 and 2 years mark to be 79% and 95%, respectively. They concluded that cyclic PDT in solid organ transplant patients may reduce the occurrence of SCCs. In addition, according to the latest European guidelines for topical PDT, one treatment of MAL-PDT has the potential to delay the occurrence of a new NMSC in OTR versus controls, 9.8 versus 6.7 months, respectively. They also noted that ALA-PDT was effective in treating 22 of 22 facial tumors in organ transplant patients (21 BCCs and 1 keratoacanthoma), using 1 to 3 treatments; however, 2 invasive SCCs did not respond. In addition, they found that both OTR and immunocompetent patients had similar clearance rates, 86% and 94%, in the short term (4 weeks) when treating AKs and Bowen disease, however, long term (48 weeks), the response rate was 48% and 72%, respectively. Finally, they noted that as a secondary prevention strategy, cyclic PDT in OTR, possibly every 3 months or twice a year, may prevent new AKs and reduce the transformation of AK to invasive SCC.⁵⁶

Basal Cell Carcinoma

Basal cell carcinoma is the most common type of skin cancer in the United States and arises from the basal cell layer of the epidermis. There are 3 major grouped variants of BCC: superficial, nodular/micro nodular, and morpheaform/sclerosing/infiltrative. Superficial BCC is defined by superficial basaloid cell buds. Aggregated basaloid cells that invade the dermis define nodular BCC and smaller clusters define micronodular BCC. In morpheaform BCC, cords of basaloid cells extend between collagen bundles.

Multiple studies have examined the efficacy of ALA and MAL-PDT in the treatment of BCC. The average weighted complete clearance rates from 12 studies with follow-up periods between 3 and 36 months were 87% for superficial BCC and 53% for nodular BCC.⁶ Morton and colleagues⁵⁷ found that an incubation of 6 hours with ALA was better than a 4-hour

incubation, and red light (630 nm) was more efficacious than green light (540 nm). Szeimies and colleagues⁵⁸ compared MAL-PDT with simple excision in the treatment of superficial BCC. They treated 196 patients with 2 sessions of MAL-PDT, repeated 1 week apart, and again at 3 months, as necessary. Methyl aminolevulinate was applied under occlusion for 3 hours followed by irradiation with narrow-band red light (630 nm, 37 J/cm²). They concluded that MAL-PDT and simple excision offer similarly high efficacy, but MAL-PDT provided a much better cosmetic outcome.

Fernandez-Guarino and colleagues⁵⁹ described their 6-year experience in treating BCC with MAL-PDT and red light undergoing 2 sessions, 2 weeks apart. They reported a complete treatment response rate of 95% for superficial BCC, 49% for nodular BCC, and 46% for morpheaform/infiltrative. They also found that some anatomical areas had higher response rates. The cheeks had a 100% response rate and the scalp had an 84% response rate; the chin, lips, forehead, and temples had much lower response rate ranging from 50% to 61% respectively. Furthermore, while the dorsum of the nose had a 92% response rate, the tip of the nose and wings had a response rate of 44% and 57%, respectively. They concluded that the BCC histological type was the most important factor in predicting response to PDT therapy, with superficial BCC significantly more likely to respond to than the other histological types.

Several authors have used laser-assisted PDT to increase the delivery of the photosensitizer and increase treatment efficacy. Shokrollahi and colleagues evaluated the treatment of 110 patients with 177 BCCs, mainly on the head and neck with combined therapy using a fractional CO₂ laser and MAL-PDT.²⁴ The histological subtypes included superficial (34), nodular (50), infiltrative (9), morpheaform (7), and mixed (3), and in 74 cases the subtype was not classified. Each patient was initially treated with the CO₂ laser (150 mJ, 10 Hz, 2-mm collimated beam), followed by incubation with MAL for 3 hours and irradiated with either red light (631 nm, 37 J/cm² for 7 minutes 24 seconds) or IPL (80 J/cm², double pulsed at 40 J/cm², or pulse train of

15 impulses each with a duration of 5 milliseconds using a 610–950-nm filtered handpiece). The PDT treatment was repeated 1 week later. The mean follow-up period was 32.2 months, with a range of 7.7 to 68.5 months. They noted that all of the lesions initially treated responded, with a total recurrence-free rate of 97.1%. Only a single cycle of treatment was required in 88.1% lesions. The overall recurrence rate was 2.82%. However, 2 of the 7 morpheaform lesions recurred. They did not encounter any major adverse events, but noted mild hypopigmentation in less than 5% of patients. Patients also reported that the laser treatment was less painful and had better subjective cosmetic outcomes. They concluded that the combined CO₂ laser and PDT treatment has comparable efficacy to surgical excision in the treatment of non-complicated BCCs, especially in the nodular and superficial subtypes, with potentially better cosmetic outcomes.

Haak and colleagues evaluated the efficacy and safety of fractional CO₂ laser followed by PDT versus conventional PDT in the treatment of high-risk nodular BCC.²⁵ High-risk tumors were defined as those having a morpheaform or infiltrative histological pattern, thick tumors (>7 mm), tumors with diameter >15 mm on the face, scalp, and extremities, and >20 mm on the trunk, along with tumors located in the central face, especially around the eyes, nose, lips, and ears. A total of 32 patients were recruited. Each lesion was initially debulked, followed by either fractional CO₂ and MAL-PDT, or 2 treatments of conventional PDT, 1 week apart. The fractional CO₂ treatment protocol included 2 stacked pulses of 40 mJ, 5% density and 1,000 μ m ablation depth; the MAL was applied under occlusion for 3 hours and illuminated with red light (633 nm, 37 J/cm²). Lesions were clinically assessed at 3, 6, 9, and 12 months; biopsies were taken at 12 months. The clinical cure rates at 3 months of the CO₂-PDT and conventional PDT were 100% and 88%, respectively. However, clinical recurrences did start to occur later in the study, but remained lower in the CO₂-PDT group compared with the conventional PDT group, and were found to be 19% and 44%, respectively, at 12 months. Nevertheless, histologically at 12 months, both groups had a similar recurrence rate of 63% and 56%, respectively. They

concluded that although both CO₂-PDT and conventional PDT offered good short-term cure rates, they lacked long-term cure rates, and CO₂-PDT needs further refinement.

In clinical practice, PDT is commonly used to treat small uncomplicated superficial BCCs. The main advantage of PDT over electrodesiccation/curettage is markedly improved appearance of PDT-treated areas, including less hypopigmentation and clinical scarring. Recalcitrant lesions may be given a repeat PDT treatment or treated with other modalities. The main disadvantage is the time commitment (3 hours of incubation period), pain, and the need for 2 treatment sessions versus one for electrodesiccation/curettage or excision. These disadvantages are often outweighed when patients have multiple superficial BCCs, Gorlin syndrome, or propensity for hypertrophic scarring. In these patients, as shown by Kabingu and colleagues,⁶⁰ antibodies to proteins in the hedgehog signaling pathway formed during treatment with PDT may improve efficacy of the treatment and decrease recurrences. They further theorized that antibody formation can be enhanced by decreasing fluence rates. Furthermore, Oseroff and colleagues demonstrated that ALA-PDT was safe, well tolerated, and effective for extensive areas of diffuse BCCs and basaloid follicular hamartomas. After 4 to 7 sessions of ALA-PDT (incubation 18–24 hours, irradiation with red light with fluences of 150 J/cm² or more), with patients receiving 1 to 3 treatments, they were able to achieve clearance rates that ranged from 85% to 98% and were durable up to 6 years.⁶¹ In addition, to further improve efficacy in these instances, 2 of the authors have used pulsed dye laser as an adjuvant light source. The typical settings on a 595-nm device are 7.5 J/cm², 10-mm spot size, and 1.5-ms pulse duration. Each lesion receives multiple passes (7–10) for total fluence of 52.5 to 75 J/cm² with a 3- to 4-mm margin around lesion. A purpuric response is typically seen and epidermal sloughing can be seen. Hundreds of lesions have been treated in our clinics, with low recurrence rates (unpublished data). It is unclear how much of the response is due to the PDT effect (which may be reduced when using lasers due to oxygen depletion) versus the destructive action of the pulsed dye itself which has been previously demonstrated to effectively

treat BCC.⁶² Two of the authors have previously demonstrated the utility of pulsed dye laser in various dermatologic disorders.^{63,64} Another scenario where PDT may be used as an adjuvant treatment in BCC may be large tumors that are poor surgical candidates where other modalities such as vismodegib are being considered. Photodynamic therapy can assist in overall tumor burden reduction.

Acne Vulgaris

Propionibacterium acnes produce an endogenous porphyrin, coproporphyrin III, which makes it an attractive target for treatment with PDT. In addition, both ALA and MAL are strongly absorbed by the pilosebaceous unit. Two studies used biopsies to examine the effect of PDT on sebaceous glands. One used a high dose (150 J/cm² using 550–700 nm light source) and the other used a low dose (13 J/cm² using 600–700 nm light source). Both of the regimens caused sebocyte suppression, but suppression by the high-dose lasted longer.^{65,66} However, the high dose with red light caused epidermal necrosis making treatment untenable. Wiegell and Wulf⁶⁷ compared the efficacy of ALA-PDT with that of MAL-PDT for the treatment of acne in a randomized, split-face, blindly assessed study. Patients underwent 1 treatment and were followed for 12 weeks. Both photosensitizers were applied for 3 hours under occlusion, followed by irradiation with red light (635 nm, 37 J/cm²). The authors found an average reduction of 59% in inflammatory lesions, in both the ALA and MAL treatment groups, but no reduction in the number of noninflammatory lesions; there was no statistical difference between the 2 drugs.

Liu and colleagues⁶⁸ compared PDT, IPL, or blue-red LED phototherapy in the treatment of 150 Chinese patients with moderate to severe facial acne vulgaris. The right side of each patient was treated, whereas the left side was left untreated as a control. In the PDT group, the 5% aminolevulinic acid was incubated for 1 hour followed by irradiation with red light (633 nm, 105 mW/cm²) for 20 minutes at each visit. Treatment was repeated weekly. In the IPL group, patients were treated weekly using a density of 11 to 15 J/cm², wavelength of 420 nm, and pulse durations of 30 to

40 ms. In the last group, patients were treated with a combined blue–red light system twice weekly; blue light (415 nm, 40 mW/cm²) was administered for the first 20 minutes followed by red light (633 nm, 105 mW/cm²) for 20 minutes. Each therapy was continued until $\geq 90\%$ clearance was achieved. They found that the mean number of sessions required to achieve $\geq 90\%$ clearance in the PDT group was 3 ± 1.52 , 6 ± 2.15 sessions in the IPL group and 9 ± 3.34 sessions in the LED group. One month after the start of treatment, they found that clearance or moderate improvements were seen in 46 (92%) patients in the PDT group, compared with 29 (58%) in the IPL group and 22 (44%) in the LED group. After 3 months, minimal papules and pustules were observed in 4 patients in the PDT group, 7 in the IPL group, and 12 in the LED group, but no nodular pustules recurred. They concluded although the 3 methods were all efficacious in the treatment of acne, PDT required the least number of sessions.

In a review of PDT studies for treatment of acne by Sakamoto and colleagues,⁶⁹ the authors concluded that incubation periods of at least 3 hours were associated with long-term remission, high-dose ALA-PDT and MAL-PDT (with an incubation period of at least 3 hours, high fluence, and red light) have similar efficacy, and red light is more likely to destroy sebaceous glands than blue light or pulsed light. In addition, Yin and colleagues⁷⁰ evaluated the efficacy of combining ALA-PDT and ablative fractional Er:YAG laser (2,940 nm) in the treatment of 40 patients with scarring secondary to acne. Patients were incubated in 15% ALA under occlusion for 2 hours followed by red light (633 nm, 126 J/cm²) for 20 minutes, which was repeated every 10 days for 4 sessions. One month later, patients were treated with an ablative fractional 2,940 nm Er:YAG laser (1,600–1,800 mJ/pulse, pulse length 2 ms, 4–5 stacked laser passes) at 4-week intervals for a total of 5 treatments. Patients were evaluated at 1, 3, 6, and 12 months posttreatment. The authors noted significant reduction at all the post-treatment evaluations and noted an 80% overall improvement in acne scars. At the 12-month evaluation, they found that none of the patients had any recurrent inflammatory acne lesions and an 85% improvement in hypertrophic/atrophic scars rated

good to excellent. They concluded that the combination was a promising option to both prevent acne and improve scar formation.

A 2014 evidence-based review of PDT in the treatment of acne, by Zheng and colleagues,⁷¹ examined the effects and safety of PDT in the treatment of acne. They included 14 randomized controlled trials with 492 patients. The photosensitizers used included ALA, MAL, and indole-3-acetic acid (IAA), and light sources used were red light, PDL, IPL, long-pulsed dye laser (LPDL), and green light. They found that the following protocols were most efficacious in treating inflammatory acne lesions: ALA + red light, ALA + PDL, ALA + IPL, MAL + red light, and MAL + LPDL. However, ALA + red light was also effective in reducing sebum production and treating noninflammatory lesions, whereas ALA + IPL and IAA + green light were effective in significantly reducing sebum production. Moreover, they also noted that triple treatment protocols were very effective in improving both inflammatory and noninflammatory lesions when compared with a 2-treatment protocol; that is IR LED followed by ALA + LED was compared with ALA + LED alone. Lastly, they found that the treatment efficacy could be improved by increasing ALA concentration, ALA incubation time, PDT sessions, dose of light source, or occluding the photosensitizers. The most commonly reported adverse events associated with the PDT treatments were pain, burning or an itching sensation of the skin, erythema, and edema, which generally resolved within several hours and were tolerated. In addition, when postinflammatory hyperpigmentation was noted, it usually resolved within several months.

In clinical practice, treatment of acne with PDT is an important modality (Figures 7 and 8). The efficacy for inflammatory lesions is superior to antibiotics in most cases, but inferior to isotretinoin. Thus, it is a useful treatment option for patients with moderate to severe inflammatory acne who are poor candidates for isotretinoin. Noninflammatory lesions do not seem to be affected, which can be treated with adjunctive retinoids or physical extraction. Limitations include time commitment, cost, discomfort during treatment, posttreatment erythema, and crusting. There is no widely accepted protocol for treating inflammatory

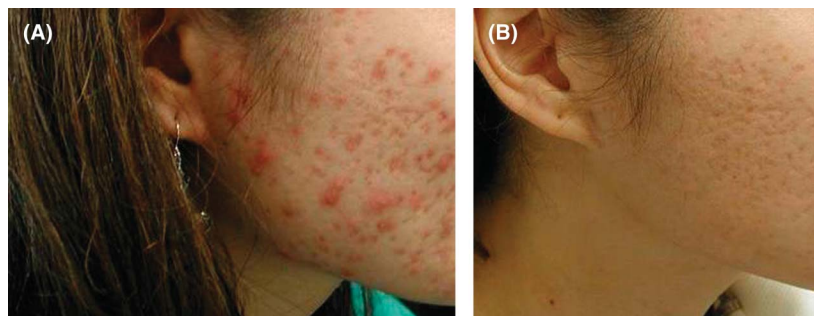


Figure 7. Acne (A) before and (B) after treatment with several sessions of PDT using 20% aminolevulinic acid and blue light (courtesy of David M. Ozog, MD).

acne patients. Increased incubation times result in improved outcomes but increase short-term side effects such as edema, pain, and inflammation. Some practitioners still opt for 2- to 3-hour incubation time with the understanding that patients will have downtime that may last for a few days. Pulsed dye laser (PDL) may be used alone with ALA/MAL or in addition to red/blue light PDT. As an adjuvant, it may have particular benefit for shallow erythematous early scars from previous inflammation.⁷²

Photorejuvenation

Multiple clinical studies have consistently demonstrated good to excellent cosmetic results with the use of PDT (Figure 9). Babilas and colleagues,⁷³ in a prospective, randomized controlled, split-face study, treated 25 patients with sun-damaged skin, treated with MAL, followed by irradiation with either an LED (635 nm, 37 J/cm²) or an IPL device (610–950 nm, 80 J/cm²). At 3 months, the authors found significant improvement in wrinkling and pigmentation, irrespective of the light source used. Gold and colleagues⁷⁴

evaluated short-contact (30–60 minutes) ALA-PDT using IPL as a light source, versus IPL alone in 16 patients in a side-by-side design. Patients were exposed to PDT for a total of 3 monthly treatments and followed at 1 and 3 months. The IPL treatment parameters were 34 J/cm²; cutoff filters used were 550 nm for Fitzpatrick skin Types I to III and 570 nm for Fitzpatrick skin Type IV. They found greater improvement in the ALA-PDT-IPL group, compared with IPL alone for all facets of photodamage.

The practical challenge with using PDT for photorejuvenation is the availability of multiple other proven and accepted modalities such as chemical peels, laser, and IPL. The additional time and supply costs of PDT limit it from becoming a widely used treatment option for photorejuvenation.

Verrucae

Several studies have demonstrated the high efficacy of PDT in the treatment of verrucae. Clearance rates of hand and foot verrucae have been reported in the



Figure 8. Back acne (A) before and 1 month (B) after treatment with a single session of PDT using 20% aminolevulinic acid (3 hours of incubation under occlusion with saran wrap and kept warm using a warm blanket) and activated using PDL, IPL, blue light, and red light (courtesy of Dr. Sabrina G. Fabi, MD).

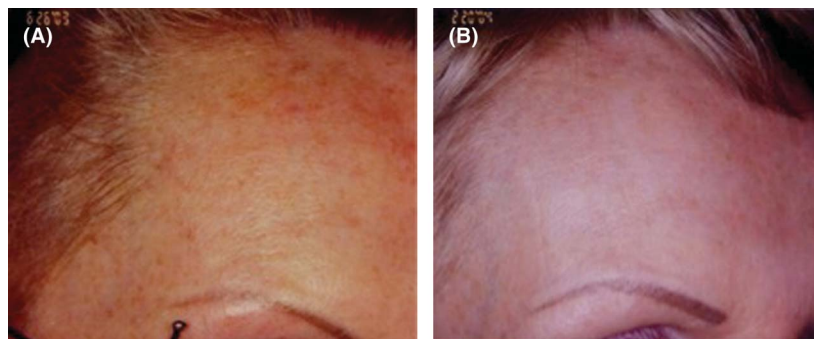


Figure 9. Solar lentigines and pigmented actinic keratosis on the forehead, before (A), and after (B) 1 treatment session of 5-ALA (1 hour of incubation) and broadband visible light source (Omnilux) (Courtesy of Nicholas J. Lowe, MD).

range of 56% to 100%. In 1 study, patients were randomized to 6 repetitive ALA-PDT or placebo-PDT treatments, performed every 1 to 2 weeks.⁷⁵ The warts were pared down before treatment, and ALA was applied under occlusion for 4 hour before irradiation with red light (590–700 nm, 70 J/cm²). At 1- and 2-month posttreatment, the median relative reduction in area with clinically apparent verrucae was 98% and 100% in the ALA-PDT group versus 52% and 71% in the placebo group. They concluded that ALA-PDT is superior to placebo-PDT in the treatment of verrucae. In another study, Schroeter and colleagues treated periungual and subungual verrucae with ALA-PDT. ALA was applied under occlusion for an average of 4.6 hours (3–6 hour) and then irradiated with red light (580–700 nm, 70 J/cm², with a range of 30–180 J/cm²).⁷⁶ They found that after an average of 4.5 treatments, total clearance was achieved in 90% of the patients.

Several studies have also examined the efficacy of PDT in the treatment of genital warts. Stefanaki and colleagues⁷⁷ treated males with condyloma acuminata with ALA under occlusion for 6 to 11 hours and then irradiated with broad band visible light (400–800 nm, 70 J/cm² or 100 J/cm²). Repeat treatment was done 1 week later for lesions that did not achieve at least a 50% improvement. At 1 year, the overall cure rate was 79.2%. In another study, Fehr and colleagues examined the efficacy PDT in the treatment of vulvar and vaginal condylomata. ALA was applied under occlusion for an average of 2.5 hours (2–4 hours), and lesions were then irradiated with dye laser coupled to a 600- μ m quartz fiber (635 nm, 116 J/cm², with a range of 100–132 J/cm²). Eight weeks after the

treatment, they reported a complete clearance rate of 66%.⁷⁸

Postcare

Immediately after PDT, patients typically develop erythema to varying degrees, which is sometimes profound in appearance. Edema is also present.⁷⁹ Pain tends to subside quickly as the illuminating light source is terminated and is thoroughly discussed later in the article.

Patients are encouraged to remain indoors and avoid being outdoors from dawn to dusk for 36 hours after the procedure. Covering with opaque clothing is the best way to avoid additional photoreactivity, as is using a wide-brim hat if stepping outside immediately after treatment and during the postoperative period. Use of mineral-based or physical sunblocks (containing zinc oxide or titanium dioxide) will not effectively block visible light on completion of PDT and during the healing phase, unless they are applied in a thick opaque coat. Most UV-blocking sunscreens, including micronized versions of zinc oxide or titanium dioxide, that are traditionally used for outdoors will not be sufficient and should not be recommended.⁸⁰ If patients feel any tingling or stinging, it is likely that they are being exposed to an ambient light source unknowingly, such as an indoor light, particularly florescent light or sunlight from a window, and are therefore encouraged to stay 6 feet away from any window. This makes daytime driving difficult without having the area physically covered posttreatment. If daylight PDT treatment becomes widely accepted, patients will only need sunscreen after application of

the photosensitizer to prevent damage from UV light. Daylight PDT is further discussed in the pain section under adverse events.

Management of Adverse Events

Pain

The mechanism of action of pain in PDT is yet to be clarified, but it is thought to be secondary to the interaction between the inflammation caused by cell necrosis and myelinated A delta or unmyelinated C fibers. Pain is often described by patients as a burning sensation, and peaks during the first few minutes of treatment. Several studies, using the visual analog scale (VAS) for pain, have demonstrated that about 20% of patients will experience a pain rated at 6 or above, which is considered significant and may lead to reduced compliance.⁸¹

Multiple factors play an important role in the amount of pain experienced. These factors include the type of photosensitizer used, location of lesions, type of lesion, amount and rate of energy delivered, type of light source, and number of sessions. Several studies have shown that MAL-PDT is less painful than ALA-PDT. This may be explained by the fact that MAL is more selectively absorbed by abnormal cells when compared with ALA.⁶⁴ It is also believed that the ALA is transported into nerve endings, whereas MAL is not. Treatment of lesions located in areas with many nerve endings, such as the head and hands, along with larger surface areas (>130 mm²), has been found to be more painful. Furthermore, the type of lesion treated may

lead to more pain; an actinic keratosis is more painful than Bowen disease or BCCs. As expected, the greater the rate and the overall energy delivered, that is irradiance and fluence, the greater the amount of pain. Studies comparing pain with different PDT light sources have generated inconsistent results; thus no firm conclusion can be made.⁶⁴ Interestingly, there is a report that the second session can be the most painful, with first session serving as a predictor of the amount of pain that the patient will experience.⁸¹ However our consensus authors have found that the first session typically causes the most discomfort and clinical reaction.

Several strategies have been studied that been found to be helpful in reducing the level of pain, but not completely eliminating it. These include cold air, topical/injectable anesthetics, reducing irradiance (including daylight PDT), and interrupting the PDT session (Table 5).

Cold Air

Cooling of the skin is the most common method of managing pain during the treatment of PDT. In addition, cold air stimulates the A delta fiber, which inhibits pain transmission. In fact, Stangland and Kroon⁸⁰ found a statistically significant difference in overall pain scores at 3 and 9 minutes, when air cooled devices were used during the treatment of actinic keratosis. However, Tyrell and colleagues found that when compared with controls, patients using cooling devices had significantly less PpIX photobleaching and reduced clinical clearance rates at 3 months. The

TABLE 5. Strategies to Manage Pain in Photodynamic Therapy

<i>Method</i>	<i>Efficacy</i>	<i>Limitations</i>
Cool air	Effective in reducing pain, but does not eliminate it	May reduce clinical efficacy
Injectable anesthetics (without vasoconstrictor)	Significantly reduces pain	Additional time and cost
Interruption of treatment (3-min break with cold spray)	Effective in reducing pain	Using cold packs may decrease efficacy
	Cold spray does not decrease efficacy	Prolong session
Topical anesthetics	Not effective	
Daylight photodynamic therapy	Effective in reducing pain	Protocols vary based on local weather. May not be practical in all locations.

authors concluded that although air cooling devices are an effective method of pain control during PDT treatment, they should be sparingly used.⁸² However, in clinical practice, cold air cooling has a clear role in decreasing patient discomfort and completing treatment sessions. To compensate for possible decreased efficacy of PDT treatment with cold air cooling, the incubation time of the sensitizer or the duration of treatment may be increased.

Injectable Anesthetics

Using either nerve blocks or local infiltration with anesthesia, without the addition of a vasoconstrictor, has been found to be helpful in managing pain in PDT treatment. Using anesthesia without a vasoconstrictor allows an adequate flow of oxygen to the treated area. Paoli and colleagues⁸³ performed unilateral facial nerve blocks in the treatment of 16 patients with symmetrically distributed facial AKs mainly on the forehead. Pain during PDT treatment was assessed by VAS. They found that pain was significantly reduced on the side treated with the facial block; the mean VAS score on the blocked side of the face was 1.3 compared with 7.5 on the nonanesthetized side. Serra-Guillen and colleagues⁸⁴ compared the efficacy of supra-trochlear and supraorbital nerve block with cold air analgesia in reducing pain experienced during PDT. They found that nerve block is superior to cold air. However, because of both additional time and cost, use of injectable anesthetics is typically reserved for cases when other noninvasive methods for anesthesia have failed.

Interruption of Treatment

Interrupting PDT for an interval of 3 minutes and spraying the patient with cold water to help cool the area being treated significantly reduce pain and do not decrease the efficacy of the treatment. This was demonstrated by Wigell and colleagues⁸⁵ who treated 24 patients with actinic keratosis; treatments were separated by a 3-minute pause in illumination, at that time the treated sites were cooled with either cold water spray or cold water pack (CoolPack—a transparent plastic bag filled with 350 mL of water at 5°C). Using the VAS, they found that pain intensity was reduced by

1.2 points using the water spray and 1.3 points by the CoolPack, but were decreased even more after a pause in treatment (by 3.7 points in water-spray patients and 3.0 points in CoolPack patients). They concluded that the combination of cooling and a 3-minute pause resulted in a greater reduction in pain, when compared with cooling alone. Although this study did not show a decrease in efficacy with the use of cold packs, this potential effect which has occurred with use of cold air should be considered. Therefore, initial attempts to decrease discomfort should be performed with interruption but without the use of cold packs. In addition, Zeitouni and colleagues completed a retrospective study of 14 patients with 51 superficial BCCs, 73 nodular BCCs, and 3 Bowen disease. ALA was incubated for 4 hours and irradiated for 20 J/cm² (30–50 mW/cm²) and then followed by 200 to 300 J/cm² (150 mW/cm²) with red light (633 nm). They followed patients for 6 to 12 months and obtained a complete response rate of 84.1% in BCCs, 67% in Bowen disease, and 37% in nodular BCCs—these results are in line with reported outcomes. They also noted a mean score of 1.0 on the VAS. They concluded that a 2-step protocol was both effective in treating the lesions and minimizing pain.⁸⁶

Daylight-Mediated Photodynamic Therapy

Efforts to minimize patient discomfort during PDT while reducing patient and staff time spent performing PDT in a clinic setting led to the development of “daylight-mediated PDT.” The protocol for daylight-mediated PDT uses MAL in combination with sunlight which serves as the activating light source. Daylight contains both blue and red light, both of which are efficient activating wavelengths used in performing PDT. Methyl aminolevulinate is applied to the face or scalp for 30 minutes followed by sunscreen application after which the patient is instructed to walk in daylight for approximately 2 hours to achieve an effective dose of activating light. A recently published consensus article on daylight-mediated PDT for the treatment of AKs examined 4 studies to determine the efficacy of treating AKs with daylight PDT and found that the mean lesion response rate was between 75% and 79% with a mean exposure time of 150 to 244 minutes.³² In addition, in the 3 studies that were

reviewed, they found maximal pain during daylight PDT to be less than or equal to 2, on a numerical rating scale. This led them to conclude that daylight PDT was nearly pain-free. One of these studies compared the efficacy of MAL with 1.5 or 2.5 hours of daylight exposure on 120 patients, with 1,572 thin actinic keratosis located on the scalp and face. Patients were asked to expose themselves to either 1.5 or 2.5 hours of daylight, within 30 minutes of applying the MAL. Of note, patients were treated between June and October. The response rate at 3 months for thin actinic keratosis was 77% and 75% for the 1.5- and 2.5-hour exposures, respectively. The response rate was independent of the effective daylight dose, exposure duration, treatment center, time of day, or time of year. Patients tolerated the treatment well, noting a maximum VAS pain level of 1.3/5. Because the authors did not find an association between response rate and light dose or duration of daylight exposure of 1 ½ or 2 ½ hours, they recommended an exposure time of 2 hours. The mechanism by which daylight-mediated PDT reduces patient discomfort during the procedure was attributed by the authors to limiting the buildup of PpIX before and during PDT. This was accomplished by the daylight-mediated PDT protocol, which uses a short incubation period of 30 minutes before PpIX activation by daylight exposure—coupled constant activation of PpIX during daylight exposure. Additional benefits of the procedure include minimal patient time spent in the clinic, minimal staff time supervising the procedure, and no requirement for the purchase of a light source. The protocol is limited by variations in weather conditions and patient compliance in following the protocol while outside the clinic setting.

In-Office Painless Photodynamic Therapy

An alternative approach to daylight-mediated PDT is an “in-office painless PDT” protocol. Based on the observation that strategies which limit the buildup of PpIX before and during PDT are effective in reducing patient discomfort during PDT, an in-office protocol was developed. The “in-office painless PDT protocol” uses 15 minutes of ALA incubation followed by 1-hour of blue light activation. Preliminary split-face studies demonstrate equivalent efficacy in clearing AKs to 75-minute incubation followed by 1,000 seconds of

blue light activation. However, pain scores using the “painless protocol” were 0/10 versus short incubation therapy pain scores of 7/10. Clinical experience using the “in-office painless PDT protocol” in over 100 patients using the protocol as full-face monotherapy or in combination with pretreatments using topical 5-FU and imiquimod before PDT provided consistent results in terms of markedly reducing or eliminating patient discomfort during PDT. The in-office protocol eliminates weather as a variable and constant supervision guarantees patient compliance during the procedure. Large-scale clinical studies are needed to establish the optimal incubation times, duration and wavelength of light activation, use with other photosensitizers, and pre- and post-treatment protocols.

Topical Anesthetics

Topical anesthetics have shown disappointing results. Topical Eutectic Mixture of Local Anesthetics, lidocaine, tetracaine, and capsaicin have all been used; however, none of them demonstrated any benefit.⁶⁴

Phototoxicity

Phototoxicity manifesting as erythema and edema are common side effects of PDT therapy. A review by Lehman⁸⁷ of 2,031 patients treated with PDT over a 5-year-period found that 89% percent of patients experienced erythema and edema. The erythema peaks at about 1 to 2 hours after irradiation and usually resolves within 1 to 2 weeks. In rare cases, the erythema may persist for longer than 3 months. Histamine has been found to be released following ALA-PDT and peaks at 30 minutes after irradiation. However, a study by Brooke and colleagues⁸⁸ found that although cetirizine doubled the median minimal urticating dose, it did not influence the 24-hour minimal phototoxic dose or erythema dose-response. Ibboston found that 34% of patients undergoing PDT developed urticaria, but others have found much lower rates, ranging from 0.9% to 3.8%.⁸⁹ Thus, although some authors have recommended use of prophylactic antihistamines, they are not widely used.

Infection

The risk of infection is quite small, possibly because of inherent PDT antimicrobial activity. The risk has been

estimated to be less than 1%.⁶ However, the development of sterile pustules is commonly seen in acne vulgaris patients treated with PDT. Although rare, Wolfe and colleagues⁹⁰ reported 4 cases of cellulitis in the treatment of over 700 patients with PDT. All 4 patients presented with increased pain and burning 1 to 4 days after PDT treatment, and cultures of the treated site were positive for *Staphylococcus aureus*. Thus, in a patient who presents with increased pain and burning following PDT treatment, cultures of the treated site and prophylactic antibiotics against *S. aureus* are recommended. Interestingly, the recurrence of herpes simplex has been rarely reported, and prophylactic antiviral treatment is not recommended at this time.

Immunosuppression

In a murine model, topical PDT has been shown to reduce the number of epidermal Langerhans cell number starting at 1 day after application, which continued to decrease and reached a minimum level about 5 days later.⁹¹ In the same animal model, PDT has been found to reduce the delayed hypersensitivity response to 2,4-dinitrofluorobenzene at the treated site (i.e., local immunosuppression); when higher fluence was used, systemic immunosuppression was observed. However, it should be noted that transplant patients are often successfully treated with PDT for NMSC, and in human subjects, no report of clinically relevant immunosuppression has been reported.

Scarring

Photodynamic therapy is usually the treatment of choice when cosmesis is of concern in the treatment of superficial NMSC.⁶ Atrophic and hypertrophic scars have rarely been reported, and PDT is being investigated for treatment of hypertrophic scarring. One mechanism of action is the reversal of the deregulation of TGF- β ₁/Smad-3 signaling pathway which exists in hypertrophic scars.⁹² Depending on the severity of the phototoxic reaction, milia and epidermoid cysts have been observed, but these will resolve over time.⁶ Because these side effects may occur as a result of a phototoxic reaction, it is important to be conservative in the use of the incubation time, irradiance and fluence used, and length of irradiation. As with other

treatment modalities, such as laser and chemical peels, scarring can occur if patients excoriate their lesions during the healing process. Patients should be counseled accordingly, and this information should be included in a patient information handout.

Pigmentation

Because PDT is known to cause inflammation in the treated area, changes in pigmentation are an expected outcome. Both hyperpigmentation and hypopigmentation have been reported with both MAL and ALA,⁶ but a higher incidence has been reported with ALA.⁶ This risk may be greater in patients with skin Types IV to VI. As in other cases with post-inflammatory pigmentation, this usually resolves with time. Patients should be educated about photoprotection, including the use of broad-spectrum sunscreens with SPF >30 once the acute phototoxic response has subsided. Patients should be informed that this discoloration, which can resemble a wind-burn or “bronzing,” will gradually fade with time.

Risk of Carcinogenesis

Finland and colleagues⁹³ examined the effects of PDT and psoralen and ultraviolet A on human skin using an in vivo model. They concluded that although psoralen and ultraviolet A results in accumulation and phosphorylation of p53 that can lead to DNA damage that may lead to tumorigenesis, ALA-PDT does not. However, there have been several case reports of skin cancers developing after PDT treatments, including a melanoma on an elderly patient's scalp following multiple PDT treatments, and keratoacanthoma developing after multiple treatments with ALA blue light PDT for facial actinic keratosis. It is difficult to prove causation in each case, and development of skin cancer may be coincidental. Particularly, because we are treating heavily damaged areas of “field cancerization” due to UV damage which is a contributing factor to both keratoacanthoma and melanoma. Of note, PDT is still relatively new to the field of medicine, with widespread use starting in the early 1990s. Thus, long-term follow-up of patients receiving multiple PDT treatments is recommended.

Conclusion

The field of PDT continues to advance. Sufficient data exist at this time, which demonstrate the utility of PDT in the treatment of actinic keratosis, superficial NMSC, photoaging, acne, and verrucae. Photodynamic therapy offers efficacy similar to standard treatments, with high patient tolerance and excellent cosmesis. However, PDT, unlike surgical excision, does not provide histologic control in the treatment of NMSC, and thus it is prudent to select appropriate lesions for treatment with this modality. Photodynamic therapy is generally well tolerated. While pain remains the most common adverse event reported, various effective strategies have been developed.

In Summary

These guidelines discuss optimizing outcome and minimizing complications for PDT including patient evaluation, patient information, consent, and post-PDT instructions.

- Photodynamic therapy is an effective treatment modality and is commonly used for actinic keratosis, SCC in situ (Bowen disease), superficial BCC, and inflammatory acne vulgaris.
- Various treatment protocols exist including various laser and light sources. It is likely that daylight PDT will become widely used as its efficacy, decrease in pain, and ease of use offer some advantages over devices in many latitudes.
- The use of fractional lasers and other physical devices before treatment seems to increase efficacy in almost all prospective studies and this combination is expected to increase as well.
- The management of pain associated with PDT is of great importance to ensure patient comfort.

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