REVIEW ARTICLE

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 colleagues[5] 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

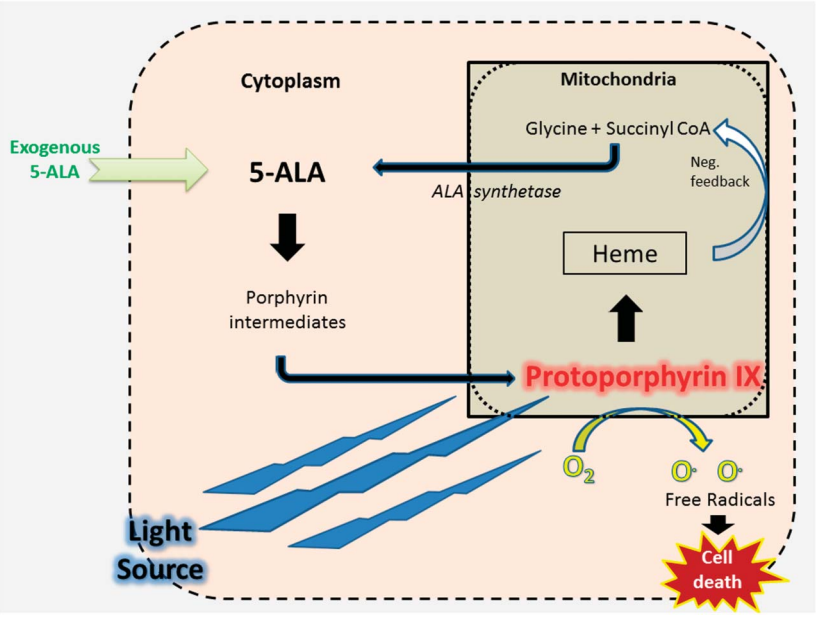

Figure 1. Mechanism of PDT. Exogenous aminolevulinic acid (ALA) enters the porphyrin-heme pathway and is converted endogenously into the PpIX. Once PpIX is activated by the proper wavelength of light, it produces singlet oxygen free radicals, which destroy the target cell (courtesy of Ali M. Rkein, MD).

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 Unites 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

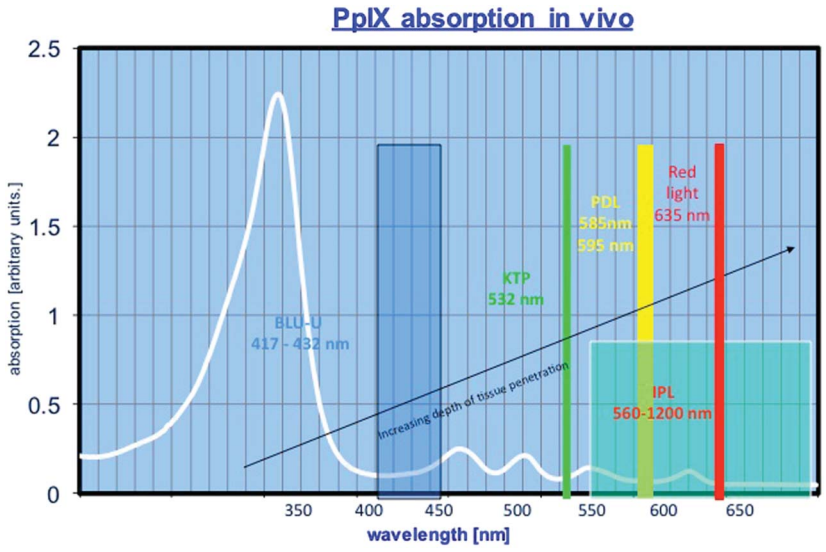

Figure 2. Absorption spectrum of PpIX in the ultraviolet and visible spectrum (courtesy of David M. Ozog, MD).

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 periprocedural details. It is imperative to obtain a proper patient medical history. Any history of photosensitizing disorders, poryphrias, 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 colleagues[26] showed equal degreasing capability between acetone and hibiclens 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 microneedling 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

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