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Abstract. Photodynamic therapy (PDT) is a noninvasive therapeutic method first introduced in the field of dermatology. It is mainly used for the treatment of precancerous and superficial malignant skin tumors. Today PDT finds new applications not only for nononcologic dermatoses but also in the field of other medical specialties such as otorhinolaryngology, ophthalmology, neurology, gastroenterology, and urology. We are witnessing a broadening of the spectrum of skin diseases that are treated by PDT. Since its introduction, PDT protocol has evolved significantly in terms of increasing method efficacy and patient safety. In this era of evidence-based medicine, it is expected that much effort will be put into creating a worldwide accepted consensus on PDT. A review on the current knowledge of PDT is given, and the historical basis of the method's evolution since its introduction in the 1900s is presented. At the end, future challenges of PDT are focused on discussing gaps that exist for research in the field. [DOI: 10.1117/1.JBO.18.6.061208]

Keywords: visible light; aminolevulinic acid; skin cancer; noninvasive; actinic keratoses; photodamage; photodynamic therapy; fluorescent diagnosis.

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1 Introduction

In the past decades, photodynamic therapy (PDT) has gained wide popularity in medicine and in dermatology in particular. Since its introduction, the procedure has evolved in terms of increasing safety and efficacy. Today PDT is used worldwide not only in the field of dermatology but also for adjuvant treatment in lung, brain, esophageal, biliary and urinary tract cancer.[1] In dermatology, this method is mainly used as a primary treatment for malignant and premalignant skin lesions, while many other nononcological applications have emerged due to the efforts of different study groups.

1.1 *Principle of PDT*

PDT is based on the photodynamic reaction: use of a light-sensitive substance (a photosensitizer), combined with light of a visible wavelength, to destroy target cells. This toxic biochemical reaction is oxygen-mediated. The photosensitizer absorbs a photon of visible light and then transfers most of the absorbed energy to a molecule of oxygen (Fig. 1). This converts it into a relatively strong oxidizing agent known as singlet oxygen. As a consequence, in the tissues that have accumulated the sensitizer, light-induced singlet oxygen exerts a cytotoxic effect by causing lethal oxidative damage to biologically important structures.

The selection of a proper photosensitizer has posed the greatest challenge in the years of PDT development. A substance that is naturally occurring offers a sufficient balance between selective tissue accumulation and relatively short clearance of the body, namely the protoporphyrin IX (PpIX). PpIX is a natural photosensitizer that can be made by the human body and is an intermediate product in the biosynthesis of heme (Fig. 2). It accumulates in rapidly proliferating cells of premalignant and malignant lesions, as well as in other structures, such as blood vessels, melanin, and sebaceous glands. In addition, malignant cells exert reduced ferrochetalase activity, resulting in excessive accumulation of intracellular PpIX.[2]

In PDT, aminolevulinic acid (ALA) or its methylated derivative—methyl-aminolevulinate (MAL)—is applied to the skin for varying periods of time, thus bypassing the rate-limiting step in the biosynthesis of heme. This leads to the conversion of ALA/MAL to PpIX. The activation of the sensitizer is accomplished by light with a specific wavelength that corresponds to the maximum absorption spectra of the sensitizer. In an ideal situation, the consecutive tissue damage is selective and only the rapidly proliferating tissue with accumulated PpIX will be destroyed with any surrounding tissue damage.

2 Historical Perspective

It was 1900 when Raab first reported the destruction of the *Paramecium caudatum* cells by exposure to combined acridine orange and light.[3] In contrast, neither the dye nor the light separately induced the cellular death. In the next decade, the extensive work of von Tappeiner contributed to the development of the concept of PDT. He first studied the photodynamic effect in protozoa by applying aniline dyes and fluorescent light.[4] One year later he described the first cases of PDT in humans by using eosin as a photosensitizer to treat a number of conditions such as condylomata lata, lupus vulgaris, and nonmelanoma skin cancer (NMSC).[5] In the later years, different photosensitizers have been introduced, and hematoporphyrin is probably the most widely studied. However, the clearance of the substance from the tissue was very slow and the phototoxic reaction persisted for a long period of time.

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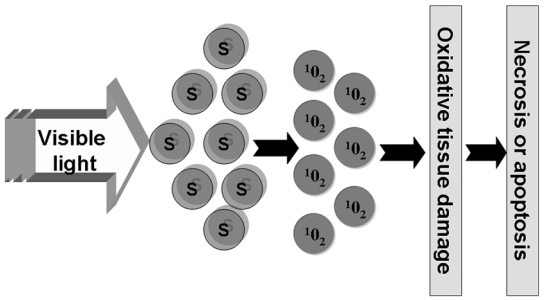

Fig. 1 Mechanism of the photodynamic reaction: the photosensitizer (*S*) is activated by the visible light. Most absorbed energy is transferred to a molecule of oxygen, which in turn is transformed into highly reactive and cytotoxic singlet oxygen ($^1O_2$). The oxidative damage is limited to the tissues rich in *S*.

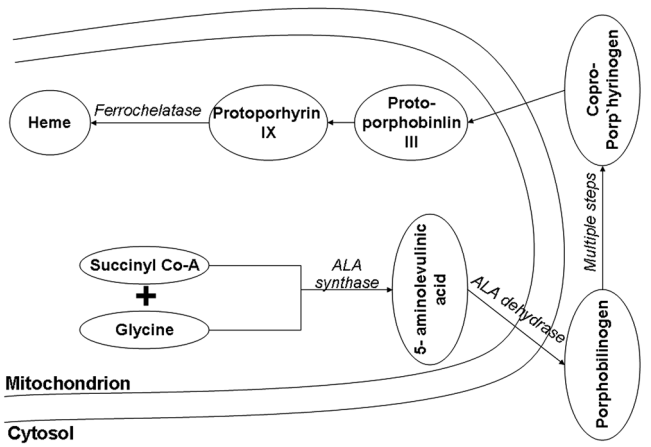

Fig. 2 Biosynthesis pathway of heme.

In the late 1970s, a new substance was introduced and recently has become a gold standard in the PDT, namely hematoporphyrin purified derivative.[6] The photoactivation was performed by visible red light, but again the accumulation in the skin lasted for up to several months. It was Kennedy in 1990 who first used ALA for topical PDT on the skin.[7] Due to the low molecular size, ALA easily penetrated the stratum corneum. In addition, it was cleared far more rapidly than the formerly used sensitizers and phototoxicity was observed only several days after the ALA application.[7]

3 Indications for PDT in Dermatology

Since its introduction, the list of PDT applications has consistently grown. Indisputably, actinic keratoses and NMSC have been the most widely used, so they will be the focus of this paper. A list of the current PDT applications is provided in Table 1.

Beyond therapeutic indications, the selective accumulation of the photosensitizer is used in the so-called fluorescent diagnostics. In this setting, the skin area of interest is illuminated by ultraviolet light (most often by using a Wood lamp) which allows the visualization of the accumulated sensitizer in the skin. The method is used in preoperative planning for the exact delineation of the tumor borders as well for control of anti-cancer therapies.[8,9]

Table 1 Applications of PDT in dermatology.

Malignant and premalignant conditions	Nononcologic skin diseases
Aktinic keratoses (and associated photodamage)	Acne
Actinic chelitis	Psoriasis vulgaris
Superficial basal cell carcinoma	Molluscum contagiosum
Superficial squamous cell carcinoma	Human papillomavirus infection
Field cancerization of the skin	Herpes virus infection
Bowen's disease	Erythrasma
Mammary and extra-mammary Paget's disease	Alopecia areata
Erythroplasia of Queyrat	Hirsutism
Cutaneous T-cell lymphoma	Sebaceous gland hyperplasia
Kaposi's sarcoma	Naevus sebaceus
Malignant melanoma	Hidradenitis suppurativa
Keratoacanthoma	Keloids and hypertrophic scars
Gorlin syndrome (multiple nevoid basasl cell carcinoma)	Pigmented purpuric dermatosis
Penile and vulvar intraepithelial neoplasia	Disseminated actinic porokeratosis
Langerhans cell histiocytosis	Erosive pustular dermatosis of the scalp
Skin metastases	Acquired perforating dermatosis
	Cutaneous sarcoidosis
	Cutaneous leishmaniasis
	Lichen planus
	Morphea
	Darier's disease (diskeratosis follicularis)
	Lichen sclerosus et atrophicus
	Lymphocytic infiltration of the skin
	Pseudepitheliomatous hyperplasia
	Skin and nail mycoses
	Acinetobacter baumannii skin infections
	Wound healing
	Photorejuvenation
	Permanent depilation

4 Factors in PDT

4.1 *Sensitizer*

Although the substances (ALA and MAL) used for local PDT in dermatology are generally referred to as photosensitizers, they are prodrugs. Once delivered to the viable epidermis, ALA/MAL is converted to PpIX, which is the endogenous photactivating agent. Within the next 24 to 48 h, PpIX is transformed to the photodynamically inactive heme.[10]

δ-5-ALA is a low molecular weight, hydrophilic molecule that can penetrate the stratum corneum and then can be included in the biosynthesis pathway of heme [Fig. 3(a)]. In the United States, ALA is marketed as 20% topical solution of hydrochloride salt. A variety of custom-made preparations as emulsions and gels are available in practice.

In addition, further substances can enhance the accumulation of PpIX, such as desferrioxamine, and the adding of DMSO and EDTA to ALA can enhance the penetration of the precursor.[11]

Esters of ALA are more commonly used in Europe. They are lipophilic derivates of ALA, which allows enhanced penetration through the lipid bilayers of the horny layer.[12] It has been shown that MAL [Fig. 3(b)] possesses better tumor selectivity and less patient discomfort compared to ALA.[13] Sixteen percent MAL cream is registered in both the United States and Europe. During photodynamic diagnosis, MAL provided higher tumor contrast than ALA in basal cell carcinoma visualization.[14] The authors concluded that MAL should be preferred for use in fluorescence diagnostics.

In recent years, new systems to carry sensitizers to the cells have been developed, such as nanostructural materials, polymeric and liposomal formulations of the sensitizers, and lipid nano-carrier-mediated nuclear targeting carriers.[15]

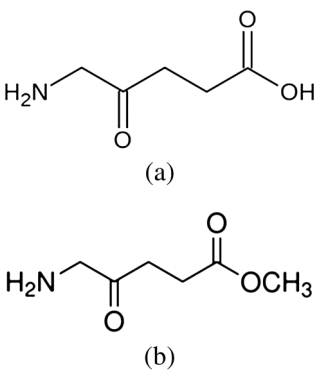

Fig. 3 Chemical formula of aminolevulinic acid (a) and methylaminolevulinate (b).

The list of substances applied in PDT is increasing and includes chlorins, bacteriochlorins, auxins, pheophorbides, purpurins, phthalocyanines, and naphthalocyanines.[16,17]

4.2 *Light Source*

Different light sources of coherent (lasers) or incoherent origin are applied in PDT. Coherence is lost within the first millimeters of penetration into the skin;[18] therefore, the use of such light sources is not an obligatory prerequisite. Furthermore the use of lasers is more expensive and can be related to some difficulties during the exploitation.[19] Incoherent light sources remain the golden standard for PDT, including a variety of broadband lamps, light-emitting diodes, and intense pulsed light systems. Table 2 summarizes the reports in the literature data about the light intensity and dosing in PDT with incoherent light sources. Beyond blue and red light, green and white light sources have also been occasionally reported in PDT.[19]

Porphyrins exhibit peak absorption at approximately 405 nm (Soret band; blue light spectrum) as well as several *Q* bands with absorption peaks in the red light spectrum. Red light exhibits deeper penetration profiles in the skin, therefore it is the only light approved for PDT of skin tumors.[16]

A recently developed protocol proposed the so-called daylight-mediated PDT for actinic keratoses.[20] In this setting, MAL is applied on the entire affected skin field and the patients are exposed to daylight with no further illumination with artificial light sources. A randomized multicenter study showed that this method is efficient even after a single treatment session.[20] A natural daylight exposure of an hour and a half was sufficient to gain efficacy. Thin lesions responded better than the moderate and thick actinic keratoses.

5 Adverse Events in PDT

PDT is generally well tolerated. The most common adverse events include pain and a burning sensation limited to the term of the irradiation and several hours afterwards. Larger irradiation areas and sites with rich innervation, e.g., the head, hands, and perineum, are associated with greater pain sensation.[13] A correlation between pain and the dose/intensity of the used light was also evidenced.[13,21] Pain is greater in a second session compared with the first as shown by a single study.[22] This could potentially cause a decrease in the patient's compliance. Different strategies for decreasing the pain in PDT have been proposed. Table 3 summarizes the pain management strategies.

Further local adverse events include erythema, edema, erosions, aseptic pustulosis, necrosis of the tumor, scarring, hyper- and hypopigmentation, and loss of hair. Several cases of contact allergic dermatitis to ALA[23] and MAL[24] have been described. Two reports describe possible coincidental association of PDT with carcinogenicity.[25] Experimental studies in mice showed

Table 2 Light dose and intensity for incoherent light sources for PDT.

Light source	Indications	Dose	Intensity
Broad spectrum red light	Oncologic diseases	100–150 J/cm^2	100–200 mW/cm^2
Broad spectrum red light	Inflammatory dermatoses	10–40 J/cm^2	50–70 mW/cm^2
Light emitting diodes	Oncologic diseases	37–50 J/cm^2	Up to 200 mW/cm^2

Table 3 Pain management strategies in PDT.

Method	Description	Efficacy	Limitation
Pre-irradiation systemic analgesia	Intake of analgesics such as metamizole, piritramide, or benzodiazepines, before the session	Limited efficacy; sometimes reanimation unit required	Possible drug interactions
General anesthesia	Short-term systemic anesthetic application	Good	Anesthetist required
Cool air	Ventilation during irradiation	Decreases pain, but does not eliminate it completely	Special equipment required
Topical anesthetics	Application of creams or gels with topical anesthetics	Limited reduction of pain	Not advised as the anesthetic might interfere with the acidity of the ALA/MAL-preparation
Injectable topical anesthetics	Infiltration anesthesia and nerve block	Effective	To be used pure, without vasoconstrictive agents in the preparation
Interrupting the session	For intervals of 3 min; spraying cold water spray in the interval	Reduction of pain	Prolongation of the session; no data on the long-term efficacy
Thermal water spray	Sprays used from the 4th hour after the session	Reduction of pain form day 3 to day 6 after PDT	No confirmatory studies; Does not deal with the pain during the irradiation session

that repetitive treatments with ALA-PDT even delay photo-induced carcinogenesis.[26]

6 Future of PDT

In the past century, PDT has been established as a safe, efficacious, and generally well-tolerated therapeutic method in dermatology. Today, devices for performing PDT in ambulatory settings are available. In our view, the five-year perspectives for PDT can be summarized into the following fields:

- *Novel sensitizer development and new carrier systems to the skin, e.g., nanotechnologies*: We are witnessing the constant development of new molecules and delivery systems. The challenge in this field would be a faster and more selective tissue accumulation of the sensitizer, as well as the shortened clearance period.
- *New light sources:* A step forward in this direction is the implementation of light-emitting-diode technologies in PDT. Decreasing the intensity of the light, and thus the subjective discomfort, in parallel to keeping the therapeutic efficacy, poses a challenge to researchers.
- *Reduction of pain during and after treatment sessions:* New physical and/or chemical (medicamentous) methods should be investigated as the major adverse event during PDT is the pain sensation. These should not interfere with the PDT procedure and pharmacokinetics of the sensitizers in the skin.
- *Standardization of PDT procedures worldwide:* Efforts in this area have been made and certain international consensus and guidelines for PDT already exist.[27] One of the major roles of such a consensus document exerts protective effects over medical practitioners as a part of the evidence-based medicine.
- *New indications for PDT:* This is an area which is constantly enriched by the multiple reports for the successive application to a variety of skin diseases. PDT has already been successfully applied in the treatment of skin infections with multi-drug-resistant microorganisms such as MRSA.[28]

The constant and dynamic development of novelties in the field is a certain guarantee for the future of PDT in dermatology.

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