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Recent advances in the prevention and treatment of skin cancer using photodynamic therapy

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Abstract

Photodynamic therapy (PDT) is a noninvasive procedure that involves a photosensitizing drug and its subsequent activation by light to produce reactive oxygen species that specifically destroy target cells. Recently, PDT has been widely used in treating non-melanoma skin malignancies, the most common cancer in the USA, with superior cosmetic outcomes compared with conventional therapies. The topical 'photosensitizers' commonly used are 5-aminolevulinic acid (ALA) and its esterified derivative methyl 5-aminolevulinate, which are precursors of the endogenous photosensitizer protoporphyrin IX. After treatment with ALA or methyl 5-aminolevulinate, protoporphyrin IX preferentially accumulates in the lesion area of various skin diseases, which allows not only PDT treatment but also fluorescence diagnosis with ALA-induced porphyrins. Susceptible lesions include various forms of non-melanoma skin cancer such as actinic keratosis, basal cell carcinoma and squamous cell carcinoma. The most recent and promising developments in PDT include the discovery of new photosensitizers, the exploitation of new drug delivery systems and the combination of other modalities, which will all contribute to increasing PDT therapeutic efficacy and improving outcome. This article summarizes the main principles of PDT and its current clinical use in the management of non-melanoma skin cancers, as well as recent developments and possible future research directions.

Keywords

5-aminolevulinic acid; ALA; MAL; methyl 5-aminolevulinate; PDT; photodynamic therapy; photosensitizers; skin cancer; topical PDT

Skin cancer is the most common form of cancer, accounting for nearly half of all cancers in the USA [1]. The most common types of skin cancer are non-melanoma skin cancers (NMSCs): basal cell carcinoma (BCC), which forms in the basal cells, and squamous cell carcinoma (SCC), which forms in the squamous cells. BCCs are rarely fatal, but can be

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highly disfiguring if allowed to grow. From the most recent estimate, approximately 2.8 million BCCs and 700,000 SCCs are diagnosed annually in the USA [2].

Genetic factors and environmental exposure to UV radiation in sunlight or tanning beds are strong risk factors for the genesis of skin cancer. Traditional skin cancer treatments including surgery, radiation therapy and chemotherapy all cause serious side effects caused by the loss of normal cell function due to nonspecific targeting of the treatments. By comparison, photodynamic therapy (PDT) is a relatively new treatment modality that involves the administration of a photosensitizing drug and its subsequent activation by light to produce reactive oxygen species that specifically destroy target cells. After the photosensitizer accumulates in target tissues, the photodynamic process is initiated with the targeted application of light at a wavelength matching the absorption wavelength of the photosensitizer. This article will review the history of and current developments in the use of PDT to prevent and treat skin cancer.

Photodynamic therapy

History of PDT

It was known thousands of years ago by ancient Egyptian, Chinese and Indian civilizations that sunlight, alone or in combination with salves, could be used to treat various diseases such as psoriasis, rickets, vitiligo and skin cancer [3–6]. However, it was not until the beginning of the 20th Century that the term ‘photo dynamic action’ was coined by Tappeiner and colleagues to describe the oxygen-consuming chemical reactions induced by photosensitization in biology [7]. Over the last 100 years, PDT has been successfully developed to treat diseases in a variety of fields, including urology (bladder cancer [8–10]), gastroenterology (stomach and esophageal cancer [11,12]), respiratory medicine (lung cancer [13,14]) and ophthalmology (age-related macular degeneration [15,16]), as well as dermatology.

In particular, PDT has grown in popularity in dermatology, mainly due to the easy accessibility of light exposure for the skin and the simplicity of topical use of photosensitizers. In the late 1970s, Thomas Dougherty initiated human clinical trials of PDT with hematoporphyrin derivative (HpD) for the treatment of cutaneous cancer metastases, including BCC and SCC [17–19]. However, there are several limitations and side effects associated with PDT treatment using HpD photosensitizers such as Photofrin® (Axcan Pharma Inc., Quebec, Canada), mainly owing to their prolonged phototoxicity. PDT has been revitalized and has become more applicable to general dermatology since 1990, when Kennedy *et al.* introduced 5-aminolevulinic acid (ALA), a topical porphyrin precursor that leads to the local accumulation of the endogenous photosensitizer protoporphyrin IX (PpIX) with no significant prolonged phototoxicity [20].

Mechanism of PDT

Photodynamic therapy requires the presence and interaction of three key elements: light, a photosensitizer and oxygen. After exposure to specific wavelengths of light, the photosensitizer is excited from a ground state (S_0) to an excited singlet state (S_1) (Figure 1). It then undergoes intersystem crossing to a longer-lived excited triplet state (T_1). Then, the photosensitizer at T_1 state can undergo two types of reaction with surrounding molecules: either a type I reaction through hydrogen or electron transfer with the production of free radicals, or a type II reaction through energy transfer to oxygen, producing singlet oxygen ($^1O_2$). The $^1O_2$ species is highly active in biological systems and can only diffuse less than 0.02 μm in a cell before deactivation during its very short lifetime (τ <40 ns) [21]. Thus, $^1O_2$-mediated damage occurs at the site of its generation and affects all intracellular components, including proteins, lipids and DNA. Although it is considered that $^1O_2$ is the

major cytotoxic species and principal initiating pathway responsible for the damaging effects of PDT, free radicals also play an important role through type I reactions for the oxidative damage mediated by PDT [22].

Light source, delivery & dosimetry

A basic law of photobiology is that the longer the wavelength of light the deeper the penetration through biological tissues. As human skin is more readily accessible to light than internal organs, dermatological applications of PDT may be able to use a wider variety of wavelengths. The commercial Blu-U® Blue Light PDT Illuminator (DUSA Pharmaceuticals, Inc., MA, USA) with light wavelengths of 405–420 nm can provide adequate photon absorption for the photosensitizer in treatment of most epidermal lesions. Red light (600–800 nm), which can deeply penetrate the skin, is ideal for dermal lesions [23–26] and is considered the 'therapeutic window' for clinical PDT treatment.

Nowadays, various light sources have been employed for PDT treatment, including lasers, solid-state light-emitting diodes (LEDs), gas discharge lamps and incandescent filament lamps [27]. At present, commonly used lasers for PDT are pulsed dye lasers (595 nm) and diode lasers (632 and 670 nm). Lasers can provide maximum effectiveness if the monochromatic emission matches the peak absorption of the photosensitizer. Their high irradiance significantly reduces therapeutic exposure time. Furthermore, the most important advantage is that lasers can be easily combined with fiber optics so that the delivery of light can be targeted exactly to internal organ tumors. However, laser equipment is usually expensive, may be low in reliability and portability, and can be costly to maintain. In addition, lasers can illuminate only small areas of the skin surface, thus limiting their use to small lesions. Therefore, lasers have not shown therapeutic advantages, especially in the treatment of dermatological diseases. The much cheaper, and more portable and practical incoherent or LED light sources are used more extensively than lasers, especially when the lesions to be treated have a broader surface. Recently, an incoherent light source, LumaCare® LC-122M (CiTec Ltd, CA, USA), has been introduced and used for PDT treatment in dermatology [28]. Samuel *et al.* have developed a device based on lightweight, wearable organic LEDs, known as a light-emitting bandage, which is potentially of use for PDT treatment of NMSC [29].

The ideal optimum light dose for PDT should cause adequate lethal effects over the targeted tumor area while minimizing damage to the adjacent normal tissues. Overtreatment causes side effects, whereas undertreatment leads to treatment failure. However, identifying the optimum dose is a much more complex issue owing to the complexity of the PDT mechanism itself, which in addition to the light dose, needs to consider the amount of photosensitizer and availability of oxygen. Until now, most PDT treatments have been performed under empirical guidelines based on previous experience; thus, many attempts to use PDT in the clinic have led to either inadequate tumor response or unacceptable complications. A successful real-time dosimetry system that would ensure more reproducible outcomes is critically needed. At present, more elegant systems of dosimetry that combine suitable experimental systems with mathematical and Monte Carlo computational models are still under investigation [30,31].

Photosensitizers

Table 1 lists the current approved photosensitizers for PDT treatments. The first-generation photosensitizers were HpD or its purified version porfimer sodium (Photofrin). Initially they were used as systemic photosensitizers and tested for cutaneous malignancies. However, systemic intravenous administration and the resultant prolonged phototoxicity, which can last 6–10 weeks, limited their use [32,33]. Second-generation photosensitizers such as

benzoporphyrin derivative monoacid ring A (Visudyne®; QLT Inc., BC, Canada), m-tetrahydroxyphenylchlorin (mTHPC; Foscan®; Biolitec Pharma Ltd, Dublin, Ireland), tin ethyl etiopurpurin, phthalocyanines and chlorins are pure compounds and are activated by light wavelengths in the range of 660–690 nm. Most importantly, they all have a lower propensity to cause prolonged photosensitivity compared with the first-generation photosensitizers [34]. Third-generation photosensitizers (not yet approved) include lutetium texaphyrin (Lutex®, Pharmacyclics, CA, USA) [35,36] and antibody-conjugated photosensitizers [37]. These drugs have absorptions of 700–800 nm, allowing deeper penetration into tissues, and can be delivered selectively to the tumor tissue.

To avoid the prolonged photosensitivity caused by systemic administration, topically applied photosensitizers have been developed for the treatment of skin cancers. The most successful commercially available topical photosensitizers are ALA and its methyl ester methyl 5-aminolevulinate (MAL). ALA-PDT using Levulan® (DUSA Pharmaceuticals) and the Blu-U light source was approved by the US FDA for the treatment of nonhyperkeratotic actinic keratoses (AKs) of the face and scalp in 1999 [24,38]; MAL (Metvix®, PhotoCure ASA, Oslo, Norway and Galderma, Paris, France) was approved in Europe for topical PDT of AK and BCC in 2001 [39,40] and in the USA in 2004 for the treatment of AK [19,23]. The endogenous photosensitizer PpIX generated from ALA or MAL can be metabolized fully to photodynamically inactive heme over 24–48 h [17,41], which dramatically reduces the adverse side effect of prolonged cutaneous phototoxicity.

Clinical applications of PDT for cutaneous neoplasia

More critically than for most other parts of the anatomy, the optimal intervention for malignancy in the skin must not only be therapeutically successful, but also achieve excellent cosmetic and functional outcomes. As it has those advantages, PDT treatment has been extensively developed as a new modality and an alternative to surgery, radiation or chemotherapy. PDT has been investigated and used with varying degrees of success in the management of various premalignant, malignant and inflammatory cutaneous neoplasias, including AK, BCC, Bowen's disease (BD; SCC *in situ*) and cutaneous lymphoma (CL).

Topical PDT is currently being widely used to treat AK and is being increasingly used in the treatment of NMSC. While data on the use of PDT are accumulating, it remains a relatively new treatment. Recent updates commissioned by the British Association of Dermatologists in multicenter randomized controlled studies demonstrated high efficacy of topical PDT for AK, BD and superficial BCC, and efficacy in thin nodular BCC, while confirming the superiority of cosmetic outcome over standard therapies [42]. Long-term follow-up studies are also available, indicating that PDT has recurrence rates equivalent to other standard therapies in BD and superficial BCC, with lower sustained efficacy than surgery in nodular BCC [43,44]. By contrast, current evidence does not support the use of topical PDT for SCC [45]. PDT can reduce the number of new lesions developing in patients at high risk of skin cancer and may have a role as a preventive therapy. Management of treatment-related pain/discomfort is a challenge in a minority of patients, and the modality is otherwise well tolerated [46–48]. Long-term studies provide reassurance for the safety of repeated use of PDT. The main recommendations and evidence assessment for the treatment of NMSC with topical PDT are briefly summarized in Tables 2 & 3.

In general, the effectiveness of PDT depends on:

- The photosensitizer used, its ability to selectively penetrate diseased tissue and the duration of the application;

- The activating light source, its ability to penetrate to the desired target and its duration of exposure;
- The type of target cells and their oxygenation status.

To be effective, the damage resulting from PDT must surpass cellular repair mechanisms, a feature referred to as the minimum photodynamic dose.

Topical PDT has been approved by regulatory authorities in 18 countries for use in at least one NMSC indication. Two photosensitizers are licensed, a formulation of ALA (Levulan) for AK, and an esterified formulation, MAL (Metvix), for AK, BD, and both superficial and nodular BCC. Although only one formulation of ALA currently has a license, other preparations have been used in clinical studies [42].

Actinic keratosis

Actinic keratoses are the most common premalignant skin lesion induced by long-term sun exposure. It is estimated that untreated AKs have up to a 20% risk of progression to SCC [49]. Topical PDT is an effective therapy for thin and moderate-thickness AKs. Many studies have reported the efficacy of treatment for AKs using topical PDT with ALA or MAL [20,44,50–56]. Clinical trials were first initiated by Kennedy *et al.* in 1990 using 20% ALA followed by a single light exposure from a 500-W filtered lamp [20]. An overall complete response rate (CRR) of 90% was observed at 3 months' follow-up. Previously reviewed open studies described clearance rates of 71–100% for facial and scalp AKs, but a lower response of 44–73% for AKs on acral sites, following a single treatment with PDT using nonlicensed ALA preparations [40]. Recently, nine randomized multicenter control/comparison studies using licensed formulations have been published for the treatment of facial and scalp AKs. In 243 patients with multiple AKs, at least 75% of lesions resolved in 77% of patients after one treatment with Levulan ALA-PDT [52].

Photodynamic therapy for AK offers therapeutic benefits; in particular, the cosmetic outcome following PDT for AK is superior to cryotherapy. In a large randomized intraindividual study of 1501 face/scalp AKs in 119 patients, Morton *et al.* compared MAL-PDT with double freeze–thaw cryotherapy, repeating treatments at 3 months if required [57]. After 24 weeks, both groups had similarly high remission rates (PDT with MAL: 89.1%; cryotherapy: 86.1%). Overall subject preference (cosmesis, efficacy and skin discomfort) significantly favored PDT. In a recently published randomized, double-blind, prospective study by Moloney and colleagues, PDT with MAL was compared with PDT with ALA in a bilateral paired comparison study of 16 patients [56]. There was no significant difference in efficacy, as measured by reduction of AK, but PDT with MAL was considerably less painful than with ALA.

Basal cell carcinoma

Basal cell carcinomas are the most common malignant tumors of the skin, arising from the basal cells of the epidermis. They are mainly located in sun-exposed areas. Given that BCCs pre-dominantly occur in the head and face, cosmetic outcome is a not insignificant factor in choosing a therapy, especially considering that the disease increasingly affects people of younger ages. Although not currently approved by the FDA, numerous studies have documented the efficacy of PDT in the treatment of BCC [58,59].

Basal cell carcinomas come in various forms that are clinically distinguishable and are divided categorically into pigmented, morphoeic, nodular and superficial. Superficial BCCs were reported to respond well to ALA-PDT, with a weighted clearance of 87% in one review of 12 studies compared with 53% for nodular lesions [60]. In one study, prior

debulking curettage achieved a clearance rate for nodular BCC of 92% compared with 0% in the control groups (curettage or PDT alone) [61]. One randomized comparison of ALA-PDT versus cryotherapy for mixed BCC showed no difference in efficacy over 1 year but superior cosmesis with PDT [62].

In order to increase the response of BCC, particularly nodular lesions, the more lipophilic methyl ester of ALA, MAL, has been used in combination with routine double PDT treatment. In a large retrospective report of MAL-PDT for BCC, where most lesions received prior debulking curettage, an initial complete response was seen in 310 lesions and 277 remained clear after 35 months, with a good or excellent cosmetic response in 98% [63].

A recent prospective uncontrolled multicenter study of 95 patients with 148 BCC lesions showed that MAL-PDT treatment of difficult-to-treat BCCs (superficial and nodular) achieved a histologically confirmed lesion CRR of 89% at 3 months while the estimated sustained lesion CRR at 2 years was 78%, at which time 84% of patients were judged to have a good or excellent cosmetic response [64]. Lesions in the H-zone and large lesions were noted to have lower sustained CRRs.

In a recent 5-year follow-up of previous multicenter randomized studies of 101 patients with small nodular BCCs amenable to simple excision, comparing MAL-PDT with standard surgical excision treatment for BCC [65], a significantly higher estimated sustained lesion response rate was found for surgery (96%) compared with MAL-PDT (76%) [66]. Over 5 years, 14% of lesions recurred after MAL-PDT versus 4% for surgery, although no further recurrences with MAL-PDT were seen after the first 3 years. Cosmetic evaluation showed significantly better results for MAL-PDT, with 87% showing a good or excellent outcome at 5 years after PDT compared with 54% in the surgical group. These results imply that while surgery remains the gold standard for the treatment of nodular BCC, MAL-PDT is effective for treatment of these lesions and exhibits a more favorable cosmetic outcome.

A similar 5-year follow-up study compared cryotherapy with MAL-PDT for the treatment of superficial BCC. The 3-month complete clinical response rates were similar for PDT (97% of 102 BCCs) and cryotherapy (95% of 98 lesions). Cosmetic outcome was superior following PDT, with an excellent or good outcome reported in 87% of the PDT group and 49% of the cryotherapy group. The estimated complete lesion response rate at 5 years was 75% in the MAL-PDT group versus 74% in the cryotherapy group, with recurrence of 22% of lesions that had initially cleared following MAL-PDT, compared with 20% after cryotherapy [43].

BD, SCC *in situ* & other unusual SCC locations

Bowen's disease, also known as 'SCC *in situ*' and named after John T Bowen, the doctor who first described it in 1912, is a neoplastic skin disease considered to be an early stage or intraepidermal form of SCC. In the past, topical ALA-PDT has cleared, on average, 86–93% of lesions of BD following one or two treatments [40].

Recently, low-irradiance LED light sources have been applied to lesions to permit ambulatory PDT [67]. Dividing doses of light into two sessions during ALA-PDT for BD has been compared with standard single illumination and achieved equivalent response rates of 88 and 80%, respectively, at 12 months, suggesting no current advantage to split illumination [68].

Topical MAL-PDT has recently been compared with the clinician's choice of cryotherapy or 5-fluorouracil (5-FU) in a multicenter randomized controlled trial of 225 patients with 275 SCCs *in situ* (MAL: 3 h; 570–670 nm; 75 J/cm^2; 70–200 mW/cm^2) [69]. A total of 3 months

after the last treatment, clearance rates were similar following MAL-PDT (86%), cryotherapy (82%) and 5-FU (83%). PDT gave superior cosmetic results compared with cryotherapy and 5-FU (good or excellent in 94, 66 and 76%, respectively). After 24 months of follow-up, 68% of lesions remained clear following PDT, 60% after cryotherapy and 59% after 5-FU [44].

Topical PDT has been reported in case reports to clear BD in unusual sites (nipple and subungual) [70–72] and where it arises in a setting of poor healing (lower leg, epidermolysis bullosa and radiation dermatitis) [73–75]. In addition, topical ALA-PDT has been observed to offer therapeutic benefit in erythroplasia of Queyrat [76,77], a form of SCC *in situ* arising on the glans or prepuce, possibly induced by human papillomavirus [78]. MAL-PDT cleared residual erythroplasia following Mohs surgery for penile SCC [79]. Paoli *et al.* observed that PDT (ALA/MAL) to ten patients with penile intraepithelial neoplasia resulted in clearance in seven patients, but later recurrence in four [80]. There was sustained clearance in the remaining patients over 46 months, including clearance of human papillomavirus DNA.

Cutaneous lymphoma

Primary CLs originate in the skin and should be distinguished from secondary skin infiltrates, which are manifestations of lymphomas of nodal or extranodal origin. These rare diseases include various lymphoproliferative disorders: cutaneous T-cell lymphomas, cutaneous B-cell lymphomas and some rare subtypes. As a definitive cure is often impossible, it is important to control the disease and alleviate symptoms. Patients with early-stage disease limited to the skin usually require skin-directed therapies. The effectiveness of PDT has been widely studied in smaller patient cohorts [81,82]. Especially in patients with solitary lymphoma lesions, treatment options are needed that have few side effects.

In recent studies by Zane and colleagues, five patients with unilesional mycosis fungoides that had not responded to numerous other therapies received MAL-PDT [83]. Three of the patients had complete remission after only one or two sessions. Two patients had to be treated repeatedly, one requiring six and the other nine sessions, with only partial remission being achieved in the latter patient. There was no recurrence during the follow-up period of 12–34 months.

A recent study by Mori *et al.* used ALA-PDT and red light at the standard dose used for BCC to treat three patients once or twice with single early cutaneous B-cell lymphoma lesions [84]. Complete remission was achieved in all three patients. The follow-up observation period was 8–24 months.

PDT in organ transplant recipients

Long-term survival after organ transplantation is increasing; as a result, many organ transplant recipients (OTRs) have long-term complications of transplantation. Adequate graft function requires life-long immunosuppressive treatment, and the resultant modification of the immune system is associated with an increased risk of various cancers, particularly those involving viruses. Skin cancers are the most common malignant conditions in transplant recipients and account for substantial morbidity and mortality in those patients [85]. SCCs and BCCs account for more than 90% of all skin cancers in transplant recipients. The incidence of these carcinomas increases with the duration of immunosuppressive therapy, ultimately affecting 50% or more of fair-skinned transplant recipients. These lesions tend to be multiple and more aggressive. PDT offers the potential of treating large target sites, which may include multiple tumors, AK and preclinical skin cancers. In addition, it can provide a more satisfactory cosmetic outcome and, more importantly, may provide a means of preventing the development of skin cancer.

Clinical response rates for OTRs (n = 20) and immunocompetent (n = 20) individuals were compared in an open prospective trial of PDT for AK and BD [86]. Clinical response in both groups was similar at 4 weeks, with 86 and 94%, respectively. However, by 48 weeks the response rate in the OTRs was reduced to 48% compared with 72% in the immunocompetent patients. The reduced effectiveness of topical PDT in OTRs compared with immunocompetent individuals lends support to the importance of the role of immune response factors in its mechanism of action. In a randomized controlled trial, the same group reported an observed clearance of AK in 13 out of 17 OTRs at 16 weeks in areas treated by MAL-PDT (3 h; 600–730 nm; 75 J/cm^2; 80 mW/cm^2) [87]. Another group reported complete remission of 24 tumors (75%) in five OTRs with 32 facial tumors (21 BCC, eight AK, one keratoacanthoma and two SCC) following PDT (ALA: 3–5 h; 635 nm; 120 J/cm^2; 100 mW/cm^2) [88]. Two tumors, both SCC, were refractory to PDT.

A recent open intrapatient randomized study of 27 renal OTRs reported a significant delay in development of new lesions at sites treated with PDT (MAL: 3 h; 570–670 nm; 75 J/cm^2) compared with control sites (9.6 vs 6.8 months) [89]. By 12 months, 62% of treated areas were free from new lesions compared with 35% in control areas. However, no significant difference in the occurrence of SCC was observed in another study of PDT (ALA: 4 h; 400–450 nm; 5.5–6 J/cm^2) versus no treatment after 2 years of follow-up in 40 OTRs [90]. A less pronounced increase in keratotic skin lesions in the PDT-treated sites was apparent but not significant. Of note, in this latter study the light wavelengths used were in the violet region rather than the red, and keratotic lesions were not pretreated by curettage.

A small randomized intrapatient comparison study compared PDT (MAL: 3 h; 633 ± 15 nm; 75 J/cm^2; 80 mW/cm^2) with topical 5-FU for treatment of epidermal dysplasia in OTRs [91]. PDT (two treatments 7 days apart) was shown to be more effective and cosmetically acceptable than 5-FU (applied twice daily for 3 weeks) at 6-month follow-up, with PDT clearing eight of nine lesion areas, compared with only one of nine areas treated by 5-FU (lesional area reduction: PDT 100%; 5-FU 79%).

Skin cancer diagnosis & prevention

As shown in Figure 1, the excited singlet state of a photosensitizer may return to the ground state by emission of fluorescence. The fluorescence can be used for diagnostic purposes in tumor detection (fluorescence diagnosis [FD]). For FD in dermatology, the fluorescence of the porphyrin PpIX is generally detected after topical treatment with ALA or MAL. PpIX emits a specific red fluorescence once excited with blue light (408 nm). Since the precancerous and cancerous cells have an increased uptake of ALA/MAL, PpIX fluorescence is significantly increased compared with normal surrounding skin. The clinical application and benefit of FD with ALA-induced porphyrins (FDAP) has proven useful for various cancer diagnoses in addition to the skin (e.g., oral malignancies [92], bladder tumors [93], cervical cancer [94] and lung cancer [95]). In dermatology, FDAP can be used as a useful tool to highlight initial skin tumors or even outline ill-defined tumor margins for biopsy or excisional surgery [96,97]. Most clinical studies on FDAP have been conducted in BCCs with different fluorescence detection techniques [98–101]. Demarcation of these lesions can be a frequent problem in clinical routine since they are often located in the head and neck area where there is not much space for extensive surgery. FDAP can be recommended as a useful and easy technique that may provide precise detection and delineation of these tumors, thus reducing the amount of healthy tissue that is unnecessarily excised.

Although FDAP has been used since 1997, some potential problems and unresolved issues still remain. The precise mechanisms of the preferential accumulation of PpIX in different

tissues and numerous factors (internal and external) that may influence the fluorescence detection have not yet been fully elucidated. PpIX also accumulates in sites of inflammation, so false positives are possible. Moreover, a statistically significant number of clinical and histopathological trials is still lacking, and there are as yet no defined guidelines for dermatologists to use as routine strategies.

Early detection and elimination of premalignant lesions by FDAP and PDT could prevent the future development of skin cancers. It was reported that ALA-PDT delayed photo carcinogenesis in mice [102,103]. Recent preclinical and clinical studies suggest that large surface MAL- or ALA-PDT treatment could not only treat visible AK but also prevent the appearance of new AKs and skin cancer [104]. In addition to directly damaging target cells and their blood supply, PDT can also act as a biological response modifier by stimulating innate and adaptive immune responses and possibly by generating *in situ* anti-tumor vaccines [17,105,106]. However, the mechanisms involved in the prevention of skin cancer by ALA- and MAL-PDT are currently unknown, and the effects of PDT on the immune system have not been extensively studied and need to be further investigated to make PDT a more practical tool in dermatology.

Developments & perspectives in PDT

Besides new drug discovery (e.g., third-generation photosensitizers) for PDT, two prospective directions of development with highly encouraging results are combinations of PDT with other modalities and photosensitizer drug delivery technology.

Combination therapy

Although PDT has been used successfully for the management of a variety of tumors, it still has some major rate-limiting factors for a target-specific response, such as an observed angiogenic effect and pronounced inflammatory response after PDT treatment [107]. PDT in combination with other types of therapy is an attractive approach to addressing these untoward side effects.

Photodynamic therapy-induced hypoxia has been linked to an increase in the expression of numerous angiogenic growth factors, such as VEGF, hypoxia-induced factor 1α, COX-2, basic FGF, prostaglandin E2 and matrix metalloproteinases. Combination therapy using antiangiogenic agents (e.g., VEGF or COX-2 inhibitors) with PDT resulted in a significant reduction of PDT-induced expression of prostaglandin E2 and VEGF, as well as a marked improvement in tumoricidal response [108–110].

Unlike chemotherapy, radiotherapy or surgery, PDT can induce a strong acute inflammatory reaction, usually manifested as tumor-localized edema. This PDT-induced immune activation has the potential to favorably reverse the tumor–host relationship from one that is tumor dominated to one that is oriented against the tumor. A combination with immunotherapy could reinforce the immune response triggered by PDT and thus dramatically enhance the anti-tumor immune response [107]. Several recent clinical trials indicate that improved clinical outcomes can be obtained by a combination of ALA-PDT and immunomodulation therapy (e.g., with imiquimod cream) for the treatment of genital bowenoid papulosis and premalignant skin diseases, such as AK, BCCs and BD [111,112].

In some situations, combination therapy can be accomplished by linking the photosensitizer directly to an anticancer drug or to a specific antibody to target highly tumor-expressed receptors [28]. It will also be easily achieved by combining them using nanotechnology, which will be reviewed in detail in the next section.

Nanotechnology & PDT

Recently, nanotechnology has been explored as a novel platform for cancer diagnosis and treatment. Nanocarriers for drugs have the potential to enhance the therapeutic efficacy of a drug, since they can be engineered to modulate its release and stability, and to prolong its circulation time, protecting it from elimination by phagocytic cells or premature degradation. Moreover, nanoscale carriers can be tailored to accumulate in tumor cells and tissues, both through the enhanced permeability and retention effect, and by active targeting strategies using ligands designed to recognize tumor-associated molecular markers [113,114].

Nanoparticles may be used as a base for the construction of multifunctional nanoscale devices. These devices offer the opportunity to combine diagnostic, imaging or targeting agents with therapeutic agents in the same package. Thus far, several kinds of nanoparticles have been engineered and used in PDT applications; these nanoparticle agents range from liposomes [115], oil-based dispersions [116], polymeric particles [117] and hydrophilic polymer –photosensitizer conjugates [118] to gold nanoparticles [119]. Recently, silica-based nanoparticles have been widely developed as an efficient means for drug and gene delivery owing to their unique advantages such as small and uniform pore size, large surface area and pore volume, as well as nontoxicity and biocompatibility [120–123]. The porous structure of silica nanoparticles can not only act as a suitable carrier for hydro phobic photosensitizers, but also allow the oxygen and generated $^1O_2$ permeability that is essential for PDT [123,124].

Malignant melanoma, which forms in the melanocytes, is a less common type of skin cancer. Although melanoma accounts for less than 4% of all dermatologic cancers, it is responsible for 80% of deaths from skin cancer [125]. Existing chemotherapeutic strategies have shown little effect against metastatic melanoma. In addition, they all cause serious side effects owing to the loss of normal cell function due to nonspecific targeting of the treatments. PDT is a potential new approach for treatment of dermal melanoma. Our recent studies on PDT treatment of melanoma cells showed that the photostability, generation of $^1O_2$, and therapeutic efficiency of the photosensitizer Pc4 were significantly improved by encapsulation into porous silica nanoparticles [126]. This nanoplatform not only imparts solubility to the hydrophobic Pc4 in aqueous solution with less aggregation, but also transports Pc4 into melanoma cells efficiently. Encapsulated Pc4 fluoresces more strongly in cells than free Pc4, and remains fluorescent and photo active for longer, thus improving its potential for use in both early diagnosis and PDT treatment of melanoma. Furthermore, we believe that the surface modification of photosensitizers encapsulated in silicon nanoparticles with antibodies specific to melanoma cells will lead to better early diagnosis and targeted treatment of metastatic melanoma.

Expert commentary

Owing to its high efficacy, selectivity and superior cosmetic outcome, PDT has been increasingly gaining interest in dermatology over the last few years. PDT using the topical photosensitizers ALA/MAL is now a standard treatment modality in most dermatological clinics for the treatment of NMSCs such as AK, superficial BCC and SCC *in situ* (BD). Topical MAL-PDT is effective in nodular BCC, although with a lower efficacy than excision surgery, and may be considered in situations where surgery may be suboptimal. Primary SCC lesions of the skin are amenable to PDT treatment. Topical PDT is an effective therapy for BD, with equivalence to cryotherapy and equivalence or superiority to topical 5-FU. Its cosmetic outcome is superior to standard therapy. Topical PDT offers particular advantages for large/multiple patch disease and for lesions at poor healing sites.

These advantages of PDT treatment are also useful for countries with emerging economies that have a high demand for skin cancer treatment. The ability to treat small lesions as soon as they are detected, with few complications, seems very attractive. In the near future it will be possible to extensively develop PDT for clinical applications in these countries.

Owing to limitations in the ability to treat deep-set disease as a local treatment, PDT alone is not recommended for SCC lesions with potential for regional spread. For individuals at risk of lymphatic spread, surgical excision of the primary and nodal drainage region remains the standard of care. Although many studies have shown a good effect with the use of PDT to treat SCC *in situ* (BD), PDT is not recommended for the treatment of SCC, a potentially invasive and metastatic disease [42]. For epidermal dysplasias in OTRs, current evidence suggests that topical PDT, although showing lower efficacy than in immunocompetent individuals, may nevertheless provide a useful therapy.

Photodynamic therapy was tolerated well for CL treatment; in most cases erythema, edema, postinflammatory hyper pigmentation, local discomfort, burning and pain were reported. In rare cases, superficial blisters, erosion and ulceration occurred. Based on small studies with few patients, it seems that CL patients with localized lesions can benefit most from PDT. It is very likely that lymphocytes in the plaque are only inactivated, not eliminated, and remission periods are highly variable, therefore a regular follow-up is necessary. In addition, studies on larger numbers of patients are still needed to standardize treatment parameters.

Photodynamic therapy has also proven useful in skin cancer FD and prevention. Recent developments include the discovery of new photosensitizers, the combination of PDT with other modalities, and the exploitation of new drug delivery systems, especially those using nanotechnology; these advances will lead to even better diagnosis and targeted treatment of skin cancer in the future.

Five-year view

To date, PDT appears to have many open avenues for development. The most appealing one appears to be the discovery and introduction of third-generation photosensitizers whose properties could progressively improve the efficacy and specificity of a particular cancer therapy. Another important field of study is photosensitizer delivery technology. Both nanoparticle-based and tumor-targeted delivery technologies seem to be appealing approaches to pursue. Modifying the surface of the nanoparticles encapsulating the photosensitizers with antibodies specific to tumor cells will lead to even better diagnosis and targeted treatment of skin cancer, as well as other neoplasias. Another possibility concerns the use of PDT, not only as a standalone modality, but also in combination with surgery, and radio-, immuno- and chemotherapy. Of particular interest is the case of chemotherapy where, under specific conditions, synergy between the two therapies has been observed. Moreover, more compact, inexpensive and PDT-oriented devices are needed, including dedicated lasers, light sources and light dispensers, precise and simple dosimetric apparatus, and instruments for alternative PDT administration. Last, specifically for ALA-PDT in the skin, future progress will be achieved with the development of new compounds such as esterified ALA derivatives to enhance the penetration of ALA. Studies of systemic administration of ALA should also be performed, which may further enhance the efficacy of FDAP and PDT in dermatology.

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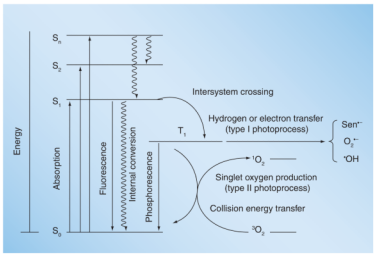

Figure 1. Photophysical process of photosensitizer after absorption of light

$^{\bullet}OH$: Hydroxyl radical; $^1O_2$: Singlet oxygen; $^3O_2$: Normal triplet oxygen; $O_2^{\bullet-}$: Superoxide anion radical; S_0: Ground state; S_1: Excited singlet state; S_2 and S_n: Higher excited states; $Sen^{\bullet-}$: Sensitizer anion radical; T_1: Excited triplet state.

Table 1

Approved photosensitizers for photodynamic therapy treatments.

Type	Chemical name	Trade name	Generic name	Country and date of approval
Systemic photosensitizers	HpD	Photofrin®	Porfimer sodium	First approved in Canada in 1993; now approved in more than 40 countries
	BPD-MA	Visudyne®	Verteporfin	Approved in the USA in 2000
	mTHPC	Foscan®	Temoporfin	Approved in Europe, Norway and Iceland in 2001
Topical photosensitizers	ALA	Levulan®	Aminolevulinic acid	Approved in the USA in 1999
	MAL	Metvix®	Methyl aminolevulinate	Approved in Europe in 2001

ALA: 5-aminolevulinic acid; BPD-MA: Benzoporphyrin derivative monoacid ring A; HpD: Hematoporphyrin derivative; MAL: Methyl 5-aminolevulinate; mTHPC: m-tetrahydroxyphenylchlorin.

Table 2

Scoring system for strength of recommendations and quality of evidence.

Score	Quality of evidence
A–E	There is A: good; B: fair; C: poor evidence to support the use of the procedure. There is D: fair; E: good evidence to support rejection of the procedure
I	Evidence obtained from at least one properly designed, randomized controlled trial
II-I	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one center or research group
II-iii	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
IV	Evidence inadequate due to problems of methodology

Table 3

Recommendations and evidence assessment for the treatment of non-melanoma skin cancer with topical photodynamic therapy.

Indication	Score	Summary of recommendations
AK	A, I	Highly effective Excellent cosmetic outcome compared with cryotherapy Should be considered as first-line therapy
BD	A, I	At least as effective as cryotherapy or 5-FU, but with fewer adverse events Good cosmetic outcome Should be considered as first-line therapy
sBCC	A, I	Effective and reliable Excellent cosmetic outcomes Useful for large, extensive and multiple lesions
nBCC	B, I	Effective and reliable for nBCC <2 mm in depth Good cosmetic outcome Long-term efficacy, with 5-year follow-up data
SCC	C, II-iii	There is insufficient evidence to support the routine use of topical PDT for SCC

5-FU: 5-fluorouracil; AK: Actinic keratosis; BD: Bowen's disease; nBCC: Thin nodular basal cell carcinoma; PDT: Photodynamic therapy; sBCC: Superficial basal cell carcinoma; SCC: Squamous cell carcinoma.