Photodynamic therapy: update 2006
Part 2: Clinical results

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Keywords
actinic keratosis, aminolevulinic acid, basal cell carcinoma, methyl-aminolevulinate, photodynamic therapy, phototherapy

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Received: 27 March 2006, accepted 11 August 2006
DOI: 10.1111/j.1468-3083.2006.02038.x

Abstract
In several randomized, controlled studies, the application of a standard preparation containing methyl-aminolevulinate (MAL; Metvix®, Galderma, F), followed by red light irradiation proved effective and well tolerated in the treatment of actinic keratosis and basal cell carcinoma, and has now been approved for clinical use in European countries. A brand name aminolevulinic acid (ALA) solution (Levulan Kerastick®, Dusa Pharmaceuticals Inc., Wilmington, MA) plus blue light exposure has been approved for the treatment of actinic keratosis in the USA. Randomized and controlled studies have shown that MAL as well as ALA are also effective in the treatment of Bowen’s disease. In addition, a large and growing number of open studies or case reports have evaluated its use in the treatment of a broad range of other neoplastic, inflammatory and infectious skin diseases. However, efficacy and definite advantages over standard therapies remain to be clarified because the experimental design of these studies was often poor, the number of enrolled patients was generally low, and the follow-up was shorter than 12 months. However, these studies have suggested a few possible clinical applications worthy of further investigation.

A growing number of laboratory and clinical findings suggest that several new synthetic sensitizers, besides ALA and MAL, may be helpful in the treatment of non-melanoma skin cancers, melanoma metastasis, and selected inflammatory and infective skin diseases. These compounds are deliverable intravenously, have short half-lives both in the blood and skin, and are highly efficient. However, they are as of yet not approved for clinical use.

Introduction
At the beginning of the 20th century, Hermann von Tappeiner coined the term ‘photodynamic reaction’ for the photochemical process involving the absorption of light by a photosensitizer and the subsequent generation of reactive oxygen species. Already at this early stage, patients with lupus vulgaris and skin malignancies were treated with photodynamic therapy (PDT). However, it took over 80 years until PDT was extensively investigated and emerged as a new promising therapeutic modality in dermatology.1 Recently, a brand name cream (Metvix®, Galderma, F) containing 160 mg/g of the methyl derivative ester (methyl-aminolevulinate, MAL) of aminolevulinic acid (ALA) has now been approved for the treatment of actinic keratosis (AK) and basal cell carcinoma (BCC) in the European Community (and also Bowen’s disease in the UK) and a 20% ALA emulsion (Levulan Kerastick®, Dusa Pharmaceuticals Inc., Wilmington, MA) has been approved in the USA for the treatment of AK. In experimental studies, both drugs also proved effective against other types of non-melanoma skin cancer (NMSC) and the number of possible clinical indications expanded outside oncology to encompass the treatment of several inflammatory and infective skin diseases.

In the same period, new ‘second-generation’ photosensitizers (e.g. benzoporphyrin derivatives, phthalocyanines, chlorines and porphycenes) have been investigated. These
synthetic dyes are chemically pure and, following topical and/or systemic delivery, have proven themselves to be highly efficient, selective and safe, while offering the advantage that the generalized skin photosensitivity they produce lasts for but a short time.

This paper aims at giving a critical evaluation of the clinical usefulness of PDT in comparison to standard treatments, and a highlight of possible relevant future developments.

**Clinical results of PDT with ALA/MAL**

**Approved uses of MAL-PDT**

Metvix has been approved by the European Community for the photodynamic treatment of AK and BCC (figs 1 and 2). Its pharmacokinetic properties have been extensively studied and an optimal treatment protocol has been standardized: Metvix is applied for 3 h, i.e. the time point of the highest ratio of porphyrin fluorescence depth to tumour depth under an occlusive and light protecting dressing before being irradiated with 75 J/cm$^2$ of red light from a high-pressure filtered lamp or 37 J/cm$^2$ of light from a diode lamp with an emission peak at 632 nm. Crusts and scales, if any, should be removed with keratolytic agents or curettage before applying this cream.

The type of curettage may deeply influence results. A deep bleeding curettage may improve the treatment results but it is painful, enhances the risk of scars and often patients refuse it without local anaesthesia. Therefore, a superficial curettage avoiding bleeding with the aim of only removing crusts and scales overlying the lesions is highly preferable.$^1$

The clinical use of Metvix has been tested in well-designed studies with prolonged follow-up, giving positive results. A European multicentre, randomized, prospective study compared MAL-PDT and cryosurgery for AK.$^3$ A total of 193 patients with 699 lesions received either a single treatment with MAL-PDT (repeated after 1 week in 8% of cases) or a double freeze-thaw course of liquid nitrogen cryosurgery. The overall complete response rates after 3 months were not significantly different: 69% with MAL-PDT and 75% with cryosurgery. The cosmetic outcomes of both MAL-PDT and cryosurgery were deemed excellent (no scarring or hypopigmentation) by 96% and 81% of the investigators, respectively, and this difference was statistically significant.$^3$

A higher (91%) overall complete response rate (after 3 months) for MAL-PDT was observed in 204 Australian patients who received two treatment sessions at weekly intervals. Clearance rates for a single treatment session of cryosurgery (68%) and placebo (30%) were significantly lower. Cosmetic outcome was rated excellent in 81% of MAL-PDT patients vs. 51% of patients treated with cryosurgery.$^4$

Similar results were found in 80 American patients with AK in a multicentre, randomized, double-blind, placebo-controlled study comparing the same MAL-PDT treatment protocol vs. a placebo. A complete response rate of 89% with two sessions of MAL-PDT and 38% with placebo were assessed at a follow-up visit 3 months after therapy. The cosmetic outcome was judged good to excellent in more than 90% of patients treated with MAL.$^5$

In a recent open prospective study, 211 patients with 413 thin to moderately thick AKs were randomized to undergo either a single treatment with PDT using topical MAL (regimen I; $n = 105$) or two treatments at weekly intervals (regimen II; $n = 106$). Thirty-seven lesions (19%) showing an incomplete response 3 months after a single treatment were re-treated. All patients were followed up 3 months after the last treatment. A total of 400 lesions, 198 initially treated once and 202 treated twice, were evaluated. The complete response rate for thin lesions after
a single treatment was 93% (95% CI = 87–97%), which was similar to 89% (82–96%) after repeated treatment. Response rates were lower for thicker lesions: 70% (60–78%) vs. 84% (77–91%), respectively. However, the overall response rate in patients randomized for the single treatment improved after the second treatment: 88% (82–94%). The conclusion of this study was that a single treatment with topical MAL-PDT is effective for thin AK; however, repeated treatment is recommended for thicker or non-responding lesions.9

Transplant patients have an increased propensity to develop multiple AKs and an increased transformation rate into invasive squamous cell carcinoma (SCC). Seventeen transplant recipients with a total number of 129 mild to moderate AKs were enrolled in a prospective, randomized, double-blind, placebo-controlled study. Two lesional areas within a patient were randomized for MAL-PDT or placebo cream plus light exposure. The lesional areas treated with MAL-PDT were clinically cleared in 13 of 17 patients, whereas placebo-treated areas did not improve.9 In an open trial from the same group, 20 transplant recipients and 20 controls with histologically confirmed AK or Bowen’s disease underwent either a single or two consecutive treatments of 20% ALA-PDT.9

This study demonstrated that PDT is also effective against AK and Bowen’s disease in immunosuppressed transplant recipients because the cure rates were comparable after 4 weeks. However, the rates were significantly lower in immunosuppressed patients after 12 and 48 weeks.7,8

A few multicentre, randomized, prospective and controlled studies of MAL-PDT of both superficial and nodular BCC have been done in the USA, Australia and Europe. In 59 patients with 350 superficial (thickness < 2 mm) BCC, the complete-clearance response rate was 89% after 3 months and 79% after a follow-up of 24–48 months (median: 35 months). Cosmetic outcome was judged as excellent or good in 98% of cases.7

A European multicentre randomized parallel-group study compared MAL-PDT to cryosurgery for the treatment of primary, histologically verified, superficial BCC. One hundred and eighteen patients were treated with a MAL-PDT treatment session or two freeze-thaw cycles. Patients with an incomplete response after 3 months were re-treated with two MAL-PDT sessions 7 days apart or cryosurgery (double freeze-thaw). The clinical remission rates of MAL-PDT and cryosurgery were 97% and 95% after 3 months, 91% and 87% after 12 months, 83% and 80% after 24 months as well as 78% and 81% after 36 and 48 months, respectively. Significantly more subjects had excellent/good cosmetic outcome with MAL-PDT than with cryosurgery (89% vs. 51%) after 3 months and similar cosmetic results were seen at each subsequent follow-up visit.10

Sixty-six patients with nodular BCC received two sessions of either MAL-PDT or placebo cream plus light exposure in a randomized, double-blind controlled study from Australia. Before MAL application, lesions were surgically debulked. The overall complete response rates were 73% for MAL-PDT and 21% for placebo after 6 months.11

In 101 patients affected by nodular BCC, two treatment sessions with MAL-PDT a week apart and surgical excision had similar overall cure rates after 3 months (91% vs. 98%). After 24 months, the recurrence rates were higher (10%) for MAL-PDT than for surgery (2%). The cosmetic outcome was good to excellent in 85% of the patients receiving MAL-PDT vs. 33% with surgery.12

Because of the excellent cosmetic results and the lack of surgical invasiveness, MAL-PDT seems particularly well suited for lesions that would otherwise require extensive surgical procedures and/or for patients with contraindications to surgery. In an open, prospective, multicentre, non-comparative study, 102 patients with ‘difficult-to-treat’ superficial and/or nodular BCC – i.e. large lesions, lesions located in the H-zone of the face or in cases where there was a high risk of surgical complications – were treated with MAL-PDT. The estimated complete response rate (assessed using a time-to-event approach) was 90% after 3 months, 84% after 12 months and 78% after 24 months. Overall cosmetic outcome was judged as excellent or good in 79% of the patients after 12 months, and 84% after 24 months.13 Similar results were obtained in 94 patients with 123 BCC lesions, who were at risk of complications or who had had poor results using conventional therapies.14

The application of a 20% ALA hydrochloride solution (Levulan Kerastick) followed within 14–18 h by irradiation with fluorescent low-pressure blue (λ<sub>peak</sub> = 407 nm) lamps (Blue-U®, Dusa) has been approved for the treatment of AK by the Food and Drug Administration in the USA.

In a randomized study of 243 patients with AKs, the use of Levulan Kerastick was compared to the vehicle alone. After periods of 8 and 12 weeks, the percentage of patients who showed a clearance of at least 75% of the treated lesions were 77% and 89% (including 30% of patients who underwent a second treatment session) in the ALA-PDT group in comparison to just 18% and 13% in the placebo group. Moderate or severe discomfort was reported by at least 90% of patients treated with Levulan Kerastick, but only 3% required discontinuation of therapy.15

In the European Community, Levulan is not yet available, but several inexpensive topical ALA preparations are on the market. However, ALA is included in the European list of orphan drugs to be used only in the photodiagnosis of bladder cancer. Therefore, the use of ALA preparations in the therapy of NMSC must be authorized by the local ethical committee.
A main drawback to studies of ALA-PDT is the lack of a standardized treatment protocol. The concentration of ALA used, the formulation of the vehicle, the methods of preparation and conservation of the final compound, the time of application, as well as many specific parameters of the light used (such as exact wavelength, duration and intensity of the various light sources) varied widely in different studies. In addition, the experimental design of the clinical trials was frequently poor: studies that were neither randomized nor controlled, or that contained a low number of enrolled patients or had only short follow-up periods. Therefore, not only the reciprocal comparison of findings between studies with ALA and those using MAL are not feasible, but the optimal treatment protocol for ALA-PDT is still unclear, and whether or not ALA-PDT can give different results from MAL-PDT is not yet known.

However, some findings of studies of ALA-PDT are of critical importance in the treatment of NMSC and are worthy of emphasis: PDT can be repeated several times and efficacy remains high even in areas with prior exposure to ionizing radiation; PDT can be used also as an adjuvant therapy in combination with Mohs' surgery; pigmented or morpheic BCC are poorly responsive even to repeated PDT sessions; BCC in Gorlin's syndrome responds in the same manner as sporadic BCC to ALA-PDT (complete response rate: 85–98% of lesions after one to three treatments per site).

Metvix is now approved in the UK, but not in other European countries, for the treatment of Bowen's disease. In previous studies ALA proved effective as well. In a bicentre, randomized, phase III trial, 40 patients with Bowen's disease (fig. 3) were randomly selected to receive either topical PDT or a cream containing 5-fluorouracil (5-FU). The PDT group was treated with 20% ALA applied 4 h before exposure to 100 J/cm\(^2\) of 630 ± 15 nm light from an incoherent light source. 5-FU was applied daily for 4 weeks. The treatment cycle was repeated after 6 weeks, if required. ALA-PDT was significantly superior to 5-FU: complete clinical clearance rates after 4 and 12 months were 88% and 82% for patients undergoing PDT and 67% and 48% for 5-FU, respectively. In the 5-FU group, a severe eczematous reaction developed around the lesions in seven cases, ulceration in three, and erosion in two. No such reactions occurred following PDT. Differences in overall pain were not observed.

Off-label applications of PDT with ALA or MAL

The use of MAL or ALA in the photodynamic treatment of skin malignancies other than AK and BCC, as well as various infectious and inflammatory skin diseases, has been reported although they have not been approved by regulatory health authorities in Europe and the USA. These studies clarified our knowledge on the mechanisms of action and on possible future applications of PDT, but the results obtained so far must be considered in most cases preliminary. In addition, possible advantages over standard treatments remain to be clarified.

Skin cancers other than AK, BCC and Bowen's disease

A few open uncontrolled trials with 20% ALA-PDT have shown contrasting results (complete clearance rates ranging from 40% to 100%) for in situ and early invasive squamous cell carcinoma (SCC) and very poor results for advanced lesions.

Therefore, ALA-PDT does not seem suitable for SCC, which, due to its metastatic potential, needs treatment
options with the highest effectiveness.\(^{21}\) In contrast, keratoacanthoma seems highly responsive to both 20%\(^{18}\) and 10%\(^{18,22}\) ALA-PDT.

ALA-PDT of Queyrat disease of the penis was effective in three patients\(^{23,24}\) but not in another case.\(^{25}\) In two further patients, a significant improvement of the condition greatly facilitated treatment by laser vaporization.\(^{23}\)

Overall results of a retrospective study of ALA-PDT on anogenital, groin and axillary extramammary Paget’s disease showed a 50% clearance rate with a high number of recurrences.\(^{26}\) However, these results are no better than those seen with standard therapies, such as Mohs’ surgery and laser.\(^{26}\)

**Skin rejuvenation and photochemoprevention of skin tumours**

The improvement of elasticity, fine wrinkles and pigmen
tary changes were registered as positive side-effects during
treatment of AKs located on severely photodamaged skin.\(^{27}\) Therefore, patients with AK who are also requesting a photorejuvenation process are ideal candidates (fig. 4). However, the treatment protocol is far from being standardized and reported studies show important differences in the concentration, formulation and mode of application of ALA or MAL, the emission spectrum, irradiance and dosage of the light source, as well as the number and frequency of treatments that should be given.

The combination of PDT with rejuvenation therapies using intense pulsed light (IPL) has been proposed as well. IPL by itself is effective against dermal and vascular manifestations of photoaging, but it is not effective against AK.\(^{27}\) With short-contact full-face 20% ALA plus IPL, more than 85% of AKs cleared and 90% of the patients achieved an overall improvement of more than 75% of their clinical symptoms of photoaging.\(^{28}\)

In a side-by-side comparison of ALA plus IPL vs. IPL alone, the combined therapy was safer and more effective for facial rejuvenation.\(^{29}\)

Photo-chemoprevention is a possible future application that is corroborated by findings obtained in mouse models where ALA-PDT protected against photocarcinogenesis by delaying ultraviolet induction of AK and SCC.\(^{30,31}\)

We assume that the mechanisms of action are the destruc
tion of tumoural lesions at their early stages, before they are clinically evident.

**Mycosis fungoides**

Unlike normal lymphocytes and their progenitors, T and B leukaemia/lymphoma cell lines are highly sensitive to ALA-PDT.\(^{32,33}\)

The enhanced accumulation of protoporphyrine IX (PpIX) in malignant lymphocytes may be related to its greater pro
duction and longer retention or the fact that it is metabolized to haem more slowly. Several metabolic and biological changes can work together to cause these effects: the activity of the rate-limiting enzyme porphobilinogen deaminase and ALA cell uptake are increased,\(^{34}\) the final biochemical step of the synthesis of haem is slowed because the activity of ferro
chelatase is decreased,\(^{35}\) and the intracellular content of iron is low, as demonstrated by the up-regulation of the transferrine receptor CD71 (OKT9),\(^{36}\) the cell cycle is fast, the pro
liferative activity is accelerated, the mitochondrial density is greater and pH values are lower than normal.\(^{37}\) Finally, an enhanced permeability of the abnormal stratum corneum overlying the plaques of mycosis fungoides can provide for an enhanced supply of ALA to the neoplastic cells.\(^{38}\)

The sensitization of skin-infiltrating malignant lymphocytes induces a selective fluorescence of mycosis fungoides plaques that was found five times more intense than in normal skin.\(^{39}\)
Overall results of trials using topical 20% ALA-PDT for mycosis fungoides seem to indicate that it is effective and well tolerated with a clearance rate that, in a few studies, was close to 100% after one to five exposures. Differences in treatment response and acute adverse effects have been reported, but they can be largely related to the small number of patients enrolled in these trials and the different PDT protocols used. The major concern against the use of PDT for mycosis fungoides is the systemic nature of the disease. In addition, PDT seems laborious and time-consuming if several or extensive lesions affecting large skin areas are present.

**Diseases of the pilosebaceous unit**

Several open prospective studies using 20% ALA reported a significant and lasting improvement of acne vulgaris, with a reduction in inflammatory lesions. The most serious adverse effects were pain, crust formation, erythema and hyperpigmentation.

Short-contact Levulan PDT and IPL or blue light (Blu-U) therapies were effective against acne and sebaceous hyperplasia and caused no or minimal pain. In 10 patients with moderate to severe acne vulgaris, the same protocol induced a partial (approximately 60%) improvement that lasted until the 3-month follow-up visit. Although the mechanisms of action of PDT in acne vulgaris are unknown, Propionibacterium acnes is susceptible to photodamage because it synthesizes an excess of endogenous porphyrins, in particular coproporphyrin III, after ALA/MAL delivery. However, the colonization of *P. acnes* is not significantly reduced in number. Sebum excretion is unchanged as well, demonstrating that the sebaceous gland is not damaged. Therefore, a reduction of the follicular obstruction by the shedding of keratinocytes and hyperkeratosis probably represents the mechanism of action here.

ALA-PDT improved significantly sebaceous hyperplasia without significant adverse effects.

Four patients with acne rosacea were studied: three were treated with MAL-PDT and one with red light alone. Lesions disappeared in the three of them who were treated with MAL-PDT (remission lasted 9 months in a patient and 3 months in the remaining two without additional or supplementary treatments). The treatment with red light alone was completely ineffective.

One patient with an extensive naevus sebaceous of Jadassohn was successfully treated with 13 treatment sessions of topical ALA-PDT.

ALA-PDT has been shown to be effective in the treatment of patients with hirsutism. Here, the efficacy was clearly relative to the dose administered: 50% improvement after 150 J/cm² and 90% after 200 J/cm².

Four patients with hidradenitis suppurativa were treated weekly for 3–4 weeks with short contact 10% ALA (Levulan) and blue light (Blu-U). They showed 75% to 100% improvement during the follow-up period that lasted for up to 3 months, and suffered no side-effects.

**Miscellaneous inflammatory skin diseases**

ALA-PDT is theoretically helpful in treating psoriasis for two reasons: first of all, it is a T-cell-mediated disease, and secondly, ALA accumulates to a greater extent in psoriatic plaques than in normal surrounding skin. However, clinical results have been disappointing so far. Ten patients, treated up to three times a week for a maximum of 12 treatments with 20% ALA plus visible light irradiation showed only a partial and unpredictable clinical improvement. PDT with 20% ALA was found less effective than narrowband ultraviolet B (NB-UVB) phototherapy in inducing both the clinical response and remission of psoriatic plaques of four patients. In a randomized, intrapatient comparison study, 29 patients were treated with 1% ALA and three different red light doses: 5 J/cm², 10 J/cm² or 20 J/cm², but the reduction of the psoriasis severity index (PSI) was always unsatisfactory. Pain during and after irradiation was a significant adverse effect in all studies and koebnerization was sometimes registered. In conclusion, ALA-PDT seems to be an inadequate treatment option for psoriasis.

PDT appears to have limited efficacy in the treatment of lichen sclerosus as well. In another preliminary study, five patients with localized scleroderma showed improvement in their clinical skin score and quantitative durometry score following repeated weekly or bi-weekly treatments with 3% ALA gel and 12 J/cm² for 3–6 months.

**Cutaneous infections**

An open study showed that, after a careful preparation, both common and flat viral warts were responsive to 20% ALA plus white light irradiation with clearance rates ranging between 56% and 100%. Cosmetic results were excellent but pain was sometimes a relevant factor.

An anecdotal case report showed that also warts of epidermodysplasia verruciformis are responsive to ALA-PDT.

Two open trials showed 95% and 100% clearance rates of condylomata. Lower efficacy (66% clearance rate) was obtained with a lower concentration (10%) of ALA plus laser (635 nm) light. Anecdotal reports seem to indicate a good efficacy for the treatment of molluscum contagiosum. However, these preliminary results do not demonstrate that ALA-PDT is superior to standard treatments for these viral skin infections.

Cutaneous leishmaniasis was successfully treated in an open trial with 10% ALA and broadband red light and in an anecdotal report with 20% MAL plus red light.
Findings of in vitro and in vivo studies have demonstrated that dermatophytes and yeasts can be effectively photosensitized by ALA. This procedure, called photodynamic antimicrobial photochemotherapy, seems to function without the hazard of causing mutagenic activity or the selection of drug-resistant strains.

**Photodynamic diagnosis with ALA or MAL**

Photodynamic diagnosis represents an effective approach to the in vivo diagnosis of dysplastic or neoplastic tissue. However, the term ‘photodynamic’ is here misleading because the ‘dynamic effect’ of PDT, which means the excitation of a photosensitizer into the triplet state and the subsequent generation of reactive oxygen species is unwanted. In fact, very low (100-fold lower as compared to PDT) light doses are delivered to excite a fluorescence of the photosensitizers selectively accumulated in the target tissues without triggering photodynamic damage.71

The clinical application and benefit of ALA-induced fluorescence has proven useful for the detection of superficial tumours of different hollow organs (e.g. bladder, gastrointestinal tract or lung,71,72) as well as the skin.

Although porphyrin fluorescence can be seen visually by the naked eye after excitation with Wood’s light, such a diagnosis is hardly specific and objective. Only a detection system capable of quantifying the fluorescence can be considered a true diagnostic tool.

By using a charge-coupled device (CCD)-camera system together with a long pass filter (to avoid interference with the bright excitation light) and a digital imaging system, the contrast of the acquired fluorescence images can be significantly enhanced in comparison to background fluorescence. In addition, this allows for the determination of a threshold through a comparison with a reference signal or a determined reference intensity, e.g. surrounding skin. Although elaborated images are often rendered as black and white gradients, a false-colour presentation makes it easier for the investigator to evaluate the distribution of the intensity of fluorescence, because the human eye can differentiate colours markedly better than it does shades of grey.71

In dermatology, photodynamic diagnosis can be used as a useful tool to highlight initial skin tumours or even outline ill-defined tumour margins for biopsy or excisional surgery.73

**Clinical results of PDT with systemic sensitizers**

**Porphyrin derivatives**

Photofrin® has been approved for the treatment of selected stages of lung, oesophageal, gastric and cervical cancer in Europe, Japan, and the USA. In several uncontrolled open trials, multiple HpD or Photofrin sessions with light doses ranging between 75 J/cm² and 200 J/cm² were effective in eradicating up to 100% of treated BCC, Bowen’s disease and SCC.74–76 However, the recurrence rate of SCC within 6 months was 50%.77

HpD (2.5–3.0 mg/kg) plus 50–200 J/cm² laser light cleared 100% of the sites treated in three77 and four78 patients with Mediterranean Kaposi’s sarcoma and Photofrin (2.0 mg/kg) and surface or interstitial delivery of 50–200 J/cm² laser light induced the total disappearance or flattening of cutaneous and mucosal nodular lesions without growth for at least 8 weeks in 58.7% treated sites of five patients with aggressive Kaposi’s sarcoma associated with AIDS.78 In another study on eight patients with AIDS-related Kaposi’s sarcoma, the same treatment protocol resulted in a 60–70% remission rate of 83 lesions, but the cosmetic results were unsatisfactory because long-lasting hyperpigmentation and scar formation occurred.79

The photosensitization of malignant T cells by HpD inhibits lymphocyte proliferation in a manner comparable to that of PUVA (psoralen–ultraviolet A) and PDT with HpD was found effective against mycosis fungoides skin lesions.80

The ability of Photofrin to photosensitize vascular tissue has been successfully exploited in pre-clinical studies for treating port-wine stains.81

As early as in 1937, PDT with systemic Hp and ultraviolet light induced a marked improvement of psoriatic plaques in seven patients.82 Almost half a century later this observation was confirmed in a patient treated with a single PDT session with HpD and 630-nm laser light. Eschars developed after PDT, but the area was reported to have healed normally.83 In another study, eight patients received low doses of Photofrin (0.5 mg/kg), several of their plaques were selected and exposed 9–20 times over the next 3–4 weeks to one of three different light sources: (690 nm argon dye laser, fluorescent UVA and 405 nm Krypton laser). Improvements of up to 85–100% were seen in patients treated with the argon dye laser.84 In 1989, in a placebo-controlled pilot study, 12 patients suffering from chronic plaque psoriasis were treated successfully with an ointment containing 1 mg/mL HpD and subsequent irradiation with ultraviolet and visible light.85

‘Second-generation’ sensitizers

Systemic zinc phthalocyanines (ZnPcs), copper phthalocyanines (CuPcs) and chloride aluminium phthalocyanines (ClAlPcs) are currently under investigation for the treatment of NMSC.86 After topical application, an amphiphilic tetracationic ZnPc has demonstrated to have a high photosensitizing activity of bacterial (including Gram-negative and multiresistant Staphylococcus aureus) and mycotic (including Candida albicans and Trychophyton
rubrum) pathogens of human skin without damaging keratinocytes.87

Intravenous delivery of benzoporphyrin derivative-monoacid A (BPD-MA), also called verteporphyrin, at doses ranging from 0.15 to 0.5 mg/kg of body weight induces an optimal photodynamic effect after 30–150 min. BPD-MA has now been approved in many countries for the treatment of a number of ophthalmologic indications, such as age-related macular degeneration. In dermatology, a single treatment with 14 mg/m² of BPD-MA was delivered to 54 patients with 421 multiple NMSCs in an open-label, randomized, multicentre phase II study.88 The absence of tumour on biopsy specimens 6 and 24 months after BPD-MA PDT ranged from 69% and 51%, respectively, in the group exposed to 60 J/cm² of red light and from 93% and 95%, respectively, with 180 J/cm². No significant systemic adverse effects were observed and 65% of tumours were judged to have good to excellent cosmesis after 24 months.88

Clinical improvement in psoriasis following PDT with intravenous BPD-MA was first reported using 690-nm light from an argon dye laser. Complete clearing of some lesions was achieved following only a single PDT session without concomitant eschar formation.89 Because lasers are expensive and impractical for treating large surfaces, subsequent studies of psoriasis with BPD-MA were performed using non-coherent light sources. Fifteen psoriatic patients received five weekly injections of BPD-MA at 8 mg/m² followed by irradiation for a 3-h period with 60 J/cm² of red light (600–700 nm). The clinical severity scores decreased from 4.0 to 2.5 and there were no significant adverse events apart from a moderate sunburn that developed on the forearms of a patient who did not comply with photoprotection precautions.90 Similar results were obtained when the same drug dose was used and the doses of UVA light were raised (20–80% of MPD).91

Four weeks after PDT with mono-L-aspartyl chlorin e6 (Npe6) was delivered in five ascending dosages ranging from 0.5 to 3.5 mg/kg body weight plus 100 J/cm² laser light, 20 of 22 BCCs (91%) showed a complete response and the therapy was well tolerated.92

Chlorin e6 at a dose of 5 mg/kg body weight induced a complete regression of melanoma skin metastases in 14 patients with no recurrence during the study period. No patient showed a systemic toxic effect.93

In phase II trials with a single administration of ethyl etiopurpurin I (SnET₂) (1.2 mg/kg body weight) and 200 J/cm² of 660 nm laser light, overall complete response rates were 75% in 121 Kaposi’s sarcoma lesions and 92% in 86 advanced breast cancer metastases with excellent cosmetic results.94

A few prospective studies have found that PDT with meta-tetra(hydroxyphenyl)chlorin (m-THPC; Foscan®) at doses ranging from 0.1 to 0.15 mg/kg body weight and 20 J/cm² of 652-nm laser light is highly effective against early stage SCC of the oral cavity and pharynx as well as vulvar intraepithelial neoplasia.95 In these cases, PDT with Foscan seems a feasible alternative to radiotherapy and surgery with less long-term morbidity. Six out of 12 patients receiving a single dose (0.100–0.129 mg/kg) of Foscan as part of a pharmacokinetic study developed partial thickness burns of the forearms after minimal exposure after 2 weeks.96 However, this was probably related to an extravasation of the drug at the time of infusion.98

Phase I studies with lutetium tetraeporphyrin and 732-nm laser light have been carried out in 19 patients with BCC, Kaposi’s sarcoma, or metastatic melanoma. Lutetium tetraeporphyrin was found to be highly selective when compared to normal skin and effective for tumours, and caused no significant phototoxicity of the skin following systemic administration.99

Topical meso-tetra-(4-sulfonatophenyl)porphine (TPPS₄) plus exposures to light at 630 nm was highly effective for the treatment of NMSCs with a complete response rate of 93.5% and a recurrence rate after 2 years of only 18–20%.100

Safety and adverse effects profile

With both topical and systemic PDT, local transitory erythema and oedema develop on the sensitized skin during light exposures and the patients may experience a burning sensation, stinging pain, or itching restricted to the irradiated area. These symptoms are usually restricted to the period of irradiation but may last a couple of hours thereafter. It is as yet unclear if there are differences in these symptoms when different sensitizers are used. Furthermore, there is no agreement on their incidence or intensity even when the same sensitizer is used. With ALA, patients with AK seem to experience more pain than patients with BCC or Bowen’s disease, and the degree of pain correlates with gender (men more than women), size of the lesion (large more than small lesions) and body site (head more than trunk and extremities), but does not depend on treatment dose, age, fluorescence intensity or Fitzpatrick skin type.101 Cooling of the lesions with a fan or spraying iced water during and soon after the treatment are widely used for reducing pain but, if an extended irradiation field or severely photodamaged skin have to be treated, the administration of oral analgesics is also necessary.102 The application of local analgesics like eutectic mixtures of lidocaine/prilocaine prior to irradiation overlapping the incubation period of ALA/MAL are not recommended as their high pH might chemically inactivate the photosensitizer.2 Indeed, topical 3% lidocaine hydrochloride did not modify the efficacy of PDT with Levulan Kerastick in 18 patients with at least four non-hypertrophic facial AKs and mild to moderate diffuse facial photodamage. However, neither did it modify their discomfort.102
Post-inflammatory hypo- or hyperpigmentation may occur after irradiation but scarring is rarely seen. Generalized skin phototoxicity is caused by the retention of detectable amounts of dyes in normal skin and it is the most relevant adverse effect with systemic intravenous sensitizers. It was intense and prolonged (up to 8 weeks) with HpD and Photofrin but it is now mild and limited to a few days when the new ‘second-generation’ sensitizers are used.

All topical and systemic sensitizers that are presently available have a negligible short-term toxicity to all healthy body organs in the absence of light exposure (this is referred to as ‘dark toxicity’). Most photosensitizers appear to be excluded from the nucleus.103 This important feature minimizes the genotoxic and mutagenic potential of PDT.

The case of an 82-year-old patient who developed a malignant melanoma on the site of repeated PDT for AKs has been reported. However, the causative connection remains unclear because the patient was previously treated with ultraviolet B phototherapy, a well-known carcinogenic agent.104 Apart from this isolated case report there has been no clinical evidence that ALA-PDT has caused secondary malignancies. Further studies are needed to evaluate the carcinogenic risk of PDT, but available data and the fact that porphyria patients do not seem to develop more malignancies than others suggest that this risk seems to be very low.103

**Conclusions**

PDT fulfills one of goals of cancer treatment: the ability to eradicate the malignant lesions while causing minimal damage to normal host cells in the treatment field and without being toxic to internal organs or causing genotoxicity and teratogenicity.

In the treatment of AK and superficial BCC, MAL-PDT is at least as effective as other types of treatment such as cryosurgery and surgery. However, MAL-PDT shows some important advantages: excellent cosmetic results, a non-invasive technique without bleeding, and local anaesthesia. It seems particularly useful in the treatment of patients with multiple lesions or wide lesions and patients with lesions in surgically difficult areas, e.g., near orifices or on the central part of the face. If results are partial or in case of relapse, MAL-PDT can be repeated several times until clinical remission occurs because it does not create a cumulative toxicity, nor does it preclude the use of other methods of treatment in the future.

PDT with ALA is another promising field but the therapeutic use of ALA in human beings has not yet been approved by the European health authorities and is therefore restricted only to experimental uses, where they have proven to be very satisfactory in the treatment of a wide number of common dermatological diseases of inflammatory, infectious or tumorous origins.

In order to enhance the efficacy and safety of systemic PDT, new synthetic, chemically pure photosensitizers with high quantum yields, absorption peaks in the range of 650–800 nm, and short serum half lives that cause limited generalized photosensitivity have been developed. Preliminary studies have investigated their clinical use against oncological and non-oncological skin diseases, but we need a wider knowledge of how to target them as well as pharmacokinetic, biological and immunological aspects before PDT can enter into daily clinical practice.

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