

Photodynamic Therapy in Dermatology

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Photodynamic therapy (PDT) uses exogenously administered or endogenously formed photosensitizers activated by light to induce cell death via formation of singlet oxygen and other free radicals. Photodynamic therapy is increasingly used for the treatment of skin cancers and other indications. The efficacy of PDT depends on the structure of the photosensitizer, the administration modality, the light source, and the treatment procedure. We reviewed the most recent clinical and experimental developments in PDT research related to dermatology. The substrate under most intense investigation in PDT research is δ -aminolevulinic acid (ALA). Photodynamic therapy with topically applied ALA has been shown to be highly efficient in the treatment of cutaneous neoplasms by using intralesionally formed porphyrins as photosensitizers. For solar keratoses, best response rates have been described. δ -Aminolevulinic-PDT is also efficient in the treatment of superficial basal cell and squamous cell carcinomas. In addition, the fluorescence of ALA-induced porphyrins under a Wood light is highly selective in neoplastic cutaneous tissue and offers a useful technique in detecting and delineating skin tumors with ill-defined borders.

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Photodynamic therapy (PDT) refers to light activation of a photosensitizer (PS) to generate highly reactive oxygen intermediates. These intermediates irreversibly oxidize essential cellular components, causing tissue injury and necrosis. For the treatment of gastrointestinal tract, cerebral, or bronchopulmonary tumors, the compounds are administered orally or intravenously.^{1,2} For the treatment of skin tumors, endometrial tumors, and bladder carcinomas (intravesical instillation), the drugs are applied mainly topically.^{1,3-5}

When PDT is used for skin diseases, topical application of the drug (eg, the porphyrin precursor δ -aminolevulinic acid [ALA]) under occlusive foil may enhance tissue penetration and avoid photobleaching. Irradiation should be performed when an optimal ratio of PS levels in tumor vs normal tissue is reached (in the case of ALA, 4-6 hours after application). The type of light

source (laser or incoherent light) and the required fluence depend on the PS used as well as the type and location of the lesion. Irradiation of porphyrin-sensitized skin areas causes erythema, severe burning, and pain, particularly on the face, possibly lasting several hours after irradiation in decreasing severity.³ Crusting is common in treated areas and disappears after a few days (**Figure 1**, C). Healing occurs within 10 to 14 days, with cosmetic results equal or superior to those of other treatment modalities, such as cryosurgery or surgery. Hyperpigmentation is common but subsides within several months in all patients.^{3,6}

PHOTOSENSITIZERS USED IN PDT

A large number of photosensitizing agents have been tested in in vitro and in

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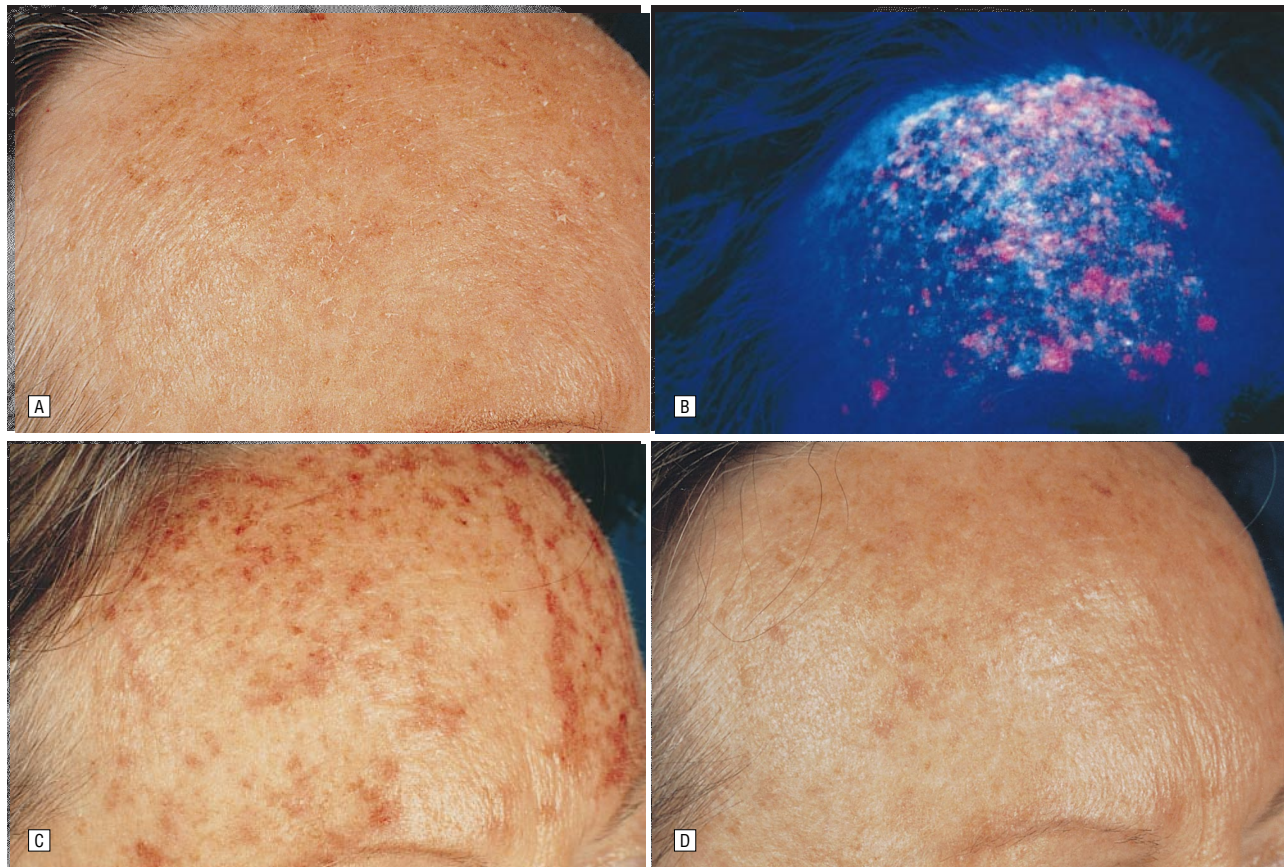


Figure 1. A, Solar keratoses in a 55-year-old woman with a history of extreme sun exposure in childhood. B, Six hours after topical application of 10% δ -aminolevulinic acid under Wood light, the neoplastic lesions are demonstrated by deep red porphyrin fluorescence. C, Three days after photodynamic therapy with δ -aminolevulinic acid (20%) and red light irradiation (120 J/cm^2). Erythema and crusting are present. D, Two weeks after photodynamic therapy. Excellent cosmetic result without residual lesions.

vivo PDT experiments (**Table 1**), but there is still no PS with ideal properties. The main classes of PSs are porphyrin derivatives, chlorins, phthalocyanines, and porphycenes.

Porfimer sodium (Photofrin II) is the only available substance for clinical use; however, its injection leads to prolonged cutaneous photosensitivity. Topical application of ALA bypasses the ALA synthase and is metabolized to porphyrins.⁷ In mouse skin, even higher fluorescence intensities were obtained with the use of ALA esters compared with free acid.⁸

Protoporphyrin IX is believed to be the predominant porphyrin metabolite induced by exogenous ALA; however, additional porphyrin metabolites such as coproporphyrin may also be induced.^{9,10} Tetrasodium-meso-tetraphenylporphyrinsulfonate is a lipophilic compound that proved highly effective in topical PDT of superficial basal cell carcinomas (BCCs) but that leads to prolonged photosensitivity.

Benzoporphyrin derivative monoacid ring A, a reduced porphyrin, has been found to be effective in treating skin tumors⁵ and psoriasis¹¹ and has further been tested in lupus erythematosus, although so far only in mice.¹² Porphycenes are synthesized porphyrins and lead to tumor remission superior to that obtained with porfimer sodium.¹³ The use of PDT with phthalocyanines, incorporating a diamagnetic metal ion to enhance triplet PS yields and lifetimes, induced tumor re-

gression superior to that with porfimer sodium. Chlorins are derived from one of the pyrrolic rings of the porphyrin macrocycle or from chlorophyll. The use of PDT with monoaspartyl chlorin e_6 led to a complete response (CR) rate of approximately 50% in skin and oropharynx cancer.¹ Meso-tetra(hydroxyphenyl)chlorin was primarily tested for diffuse interstitial tumors.² Tin etiopurpurin is supposed to produce less photosensitivity than dihematoporphyrin ether/ester.¹

METABOLISM AND PHARMACOKINETICS OF ALA

The knowledge of tissue distribution and pharmacokinetics is mandatory for a substrate that is intended for use in clinical practice.

Topical application of ALA in amounts from 0.05 to 0.2 g/cm^2 (total, 0.05-7.0 g of ALA) does not lead to measurable systemic porphyrin levels in humans.¹⁴ In contrast, in PDT with systemically administered ALA, transient increases in serum aspartate aminotransferase, nausea, vomiting, headache, circulatory failure, and prolonged photosensitivity have been reported (Alwin Goetz, MD, written communication, March 1995).^{14,15} This might be partly because of the prolonged increase in hepatic protoporphyrin level, which was shown to be 50-fold in hamsters treated with ALA, 500 mg/kg of body weight intravenously, although ALA and porphyrins were cleared rapidly from the blood and the skin.⁹

Table 1. Photosensitizers and Precursors Used in Experimental and Clinical Photodynamic Therapy Applications

Porphyrins
Hematoporphyrin derivative
Dihematoporphyrin ether/ester
Porfimer sodium
Tetrasodium-meso-tetraphenylporphyrinsulfonate
Metallo-tetra-azaporphyrin
5,20-Bis(4-sulfophenyl)-10,15-bis(2-methoxy-4-sulfophenyl)-21-thiaporphyrin (21-thiaporphyrin)
Porphyrin precursor
δ-Aminolevulinic acid (ALA)
δ-Aminolevulinic acid (ALA)-methyl-, -propyl-, -ethylester
Phthalocyanines
Chloroaluminumtetrasulfophthalocyanine
Zinc (II) phthalocyanine
Silicone naphthalocyanine
Aluminum sulfonated phthalocyanine
Porphycenes
9-Acetoxy-2,7,12,17-tetra- <i>N</i> -propylporphycene
2-Hydroxyethyl-7,12,17-tris(methoxyethyl)porphycene
23-Carboxy-24-methoxycarbonylbenzo[2,3]-7,12,17-tris(methoxyethyl)-porphycene
Bis-hydroxyethyl-7,12-di- <i>N</i> -propylporphycene
Chlorins
Monoaspartyl chlorin e_6 , diaspartyl chlorin e_6 [48V]
Anadyl-chlorin e_6 sodium, bacteriochlorin a
Chlorin e_6 monoethylene diamine-monohydrochloric acid
Benzoporphyrin derivative monoacid ring A
Pheophorbides
Pheophorbide a, bacteriopheophorbide
Others
Fluoresceins (fluorescein sodium, tetrabromfluorescein-eosin)
Anthracesenes (anthraquinone, acridine orange, yellow)
Hypericin
Furocoumarine (5-methoxypsoralen, 8-methoxypsoralen)
Chlorophyll derivatives
Purpurins (metallopurpurin, tin etiopurpurin SnET2)
Phenothiazines
Methylene blue, violet, green
Azure C, thionine, Nile blue A
Hypocrellin
Rose bengal
Tetrachlorosalicylanilide
Verdine
Rhodamine 123

The mechanism of preferential intratumoral uptake of precursors and PSs is still not fully understood. In the case of ALA, active transport is the most likely explanation, but passive diffusion may be operative as well.

The selectivity of tumor targeting may be increased by delivering the sensitizer with liposomes or tumor-specific monoclonal antibodies.¹

LIGHT SOURCES IN PDT

In general, every visible light source with suitable spectral characteristics and high output at an absorption maximum of the PS can be used in PDT.

In dermatologic applications, the most widely used light systems are the argon ion pumped dye laser (argon-PDL) (630 nm), the gold vapor laser (628 nm), and incoherent light sources emitting close to the sensitizer's absorption peaks (eg, for porphyrins, 505, 540, 580,

and 630 nm). Continuous wave (argon-PDL) and pulsed laser systems (gold vapor laser) showed equivalent tumoricidal effects. Diode lasers emitting at long wavelengths of 780 to 850 nm represent a promising development in PDT-suitable laser techniques.

In the treatment of large skin lesions, incoherent light devices are superior to laser systems. In early clinical studies, incandescent lamps or slide projectors were used. Recently, professional incoherent light devices have been developed.¹⁶ They emit at long wavelengths and may also target PSs' metabolic products with absorption peaks shifted to longer wavelengths. The most effective wavelength in ALA-PDT was found to be 635 nm.¹⁷ At low light dose, repair of sublethal damage can occur, whereas at high doses, oxygen depletion can decrease the therapeutic effect. Therefore, reduction of fluence rate or fractionated irradiation may increase PDT efficacy because of increased singlet oxygen levels in regions of sparse capillary density and reaccumulation of porphyrins in pretreated and sensitizer-bleached tissue.

As shown for our patients treated with 20% ALA for 6 hours and an incoherent light source (PDT 1200, Waldmann Lichttechnik, Villingen-Schwenninger, Germany),¹⁶ effective irradiation variables are 50 to 120 mW/cm² for solar keratoses and 150 mW/cm² for epithelial tumors, with fluences varying from 60 to 180 J/cm² (**Table 2**).

ADJUVANT THERAPEUTIC STRATEGIES

The efficacy of PDT may be increased by means of a number of adjuvants. 1,10-Phenanthroline enhances the porphyrin accumulation in cell culture.¹⁸ Deferoxamine mesylate (Desferal, Ciba Geigy, Basel, Switzerland) increases the ALA-induced porphyrin accumulation in murine squamous cell carcinoma cells and seems to improve the CR rate of BCCs in ALA-PDT.¹⁹ The use of PDT combined with hyperthermia, chemotherapeutics, vasoactive compounds, mitomycin, bioreductive substances, tumor necrosis factor α , and glucose yielded better efficacy.¹ The application of multiple PSs and irradiation with multiple wavelengths also showed an improved therapeutic outcome.¹

CURRENT STATUS OF PDT APPLICATIONS IN DERMATOLOGY

Cutaneous and Subcutaneous Tumors

In general, surgical excision is the most effective and preferred treatment of epithelial skin tumors. However, alternative modalities are necessary for extensive or multiple disseminated lesions, such as superficial BCC and solar keratoses, to improve functional and cosmetic results.^{3,20} The outcomes of clinical studies on PDT for skin tumors are generally difficult to compare, since different variables of PDT were used. The following discussion will review mainly data on topical ALA-PDT.

We apply ALA in an ointment vehicle (10%-20%; 50-200 mg/cm²) to cutaneous lesions under occlusive foil to enhance tissue penetration and to avoid photobleaching. After 4 to 6 hours, we control intralesional porphyrin formation by the emission of red fluorescence dur-

Table 2. Response of Cutaneous Neoplasms to Topical PDT With ALA and an Incoherent Light Source*

Type of Lesion and Histologic Finding	Size, cm	n	ALA, g/cm ²	Irradiation†		Response, %‡						
				mW/cm ²	J/cm ²	CR			PR			
						1	2	3	1	2	3	
Solar keratoses												
Normal	<0.5	20	0.1	50	60	60	100	...	§	25	0	...
		20	0.1	80	96	80	100	...		20	0	...
		20	0.1	120	144	95	100	...		5	0	...
	0.5-1	30	0.1	50	60	57	83	100		10	13	0
		30	0.1	80	96	67	93	100		20	7	0
		25	0.1	120	144	92	100	...		8	0	...
	>1	10	0.1	50	60	50	90	100		25	5	0
		7	0.1	80	96	86	100	...		14	0	...
		7	0.1	120	144	86	100	...		14	0	...
Transition into SCC	0.8-2.6	12	0.1	120	144	83	92	100		8	8	0
Basal cell carcinoma												
Superficial	<1	5	0.2	80	96	60	80	100		20	20	0
		5	0.2	120	144	80	100	...		20	0	...
		6	0.2	150	180	83	100	...		17	0	...
	1-2	10	0.2	80	96	70	90	90		10	10	10
		8	0.2	120	144	63	88	100		13	13	0
		10	0.2	150	180	80	90	100		20	10	0
	2-4	8	0.2	80	96	60	60	75		25	38	25
		5	0.2	120	144	80	80	80		0	20	20
		12	0.2	150	180	67	83	100		25	17	0
	4-8	9	0.2	80	96	25	50	63		13	25	25
		9	0.2	120	144	50	50	63		25	25	13
		9	0.2	150	180	50	75	75		50	25	25
	8-12	2	0.2	80	96	0	0	50		100	100	50
		3	0.2	120	144	0	0	33		66	100	66
		3	0.2	150	180	0	33	33		66	66	66
Multicentric	...	7	0.2	150	180	43	71	86		57	29	14
Sclerodermiform	...	13	0.2	150	180	61	69	85		23	23	15
Nodular	0.3-2.5	3	0.2	150	180	0	0	33		100	100	66
Exulcerated	1.2-3.8	4	0.2	150	180	0	25	50		75	75	50
Squamous cell carcinoma												
Superficial	0.8-2.6	8	0.2	80	96	38	62	62		25	25	38
	1.2-3.0	10	0.2	120	144	40	50	70		30	40	30
	0.7-2.7	10	0.2	150	180	60	80	100		40	20	0
Nodular	0.5-3.1	4	0.2	150	180	0	25	50		75	75	50
Exulcerated	1.5-2.8	4	0.2	150	180	0	50	75		40	50	25
Bowen disease	1.8-15.8	8	0.2	150	180	50	75	75		50	25	25
Bowen carcinoma	2.9-4.5	2	0.2	150	180	0	0	50		100	100	50
Keratoacanthoma	1.8-4.2	4	0.2	150	180	0	25	50		50	75	50

*PDT indicates photodynamic therapy; ALA, α -aminolevulinic acid; CR, complete response; PR, partial response; and SCC, squamous cell carcinoma.

†Irradiation was performed for 20 minutes in all cases.

‡Response rates are given for a follow-up period of 12 to 24 months. 1, 2, and 3 are numbers of treatments; PDT was performed until complete response of the lesion, but a maximum of 3 PDT sessions were applied. The interval between each treatment was 1 month.

§No data are available because no PDT was performed.

ing irradiation with a Wood light (Fluotest, Xenotest, Hanau, Germany; 370-405 nm) (Figure 1, B, and **Figure 2**, B).³ Tumors are treated with an incoherent light source (PDT 1200, 570-750 nm).¹⁶

Basal Cell Carcinoma. For systemically administered porphyrins, CR rates of 31% to 100% have been reported.^{21,22} Kennedy et al⁷ showed that topical ALA application to epithelial tumors induces the accumulation of porphyrins that results in localized fluorescence and photosensitization. A CR was achieved in 90% of approximately 80 superficial BCCs. Several other authors^{4,7,18,23-25} reported a good CR (50%-100%) for superficial BCCs to PDT with ALA. Addition of 3%

deferoxamine seems to improve therapeutic efficacy for noduloulcerative BCCs.¹⁹ However, it is important to specify that the comparison was between studies done by different investigators. In 35 patients with 100 lesions, we showed that the CR rate of superficial BCCs was dependent on the size of the lesion and proportional to the light intensity (Table 2; **Figure 3**). Tumors larger than 4 cm in diameter generally have shown a poor response to ALA-PDT even after 3 treatment sessions. In contrast to early enthusiastic clinical reports,^{24,26} histological and long-term follow-up studies showed a less favorable outcome, especially in large tumors, probably because of insufficient and inhomogeneous ALA penetration and inhomogeneous light irra-

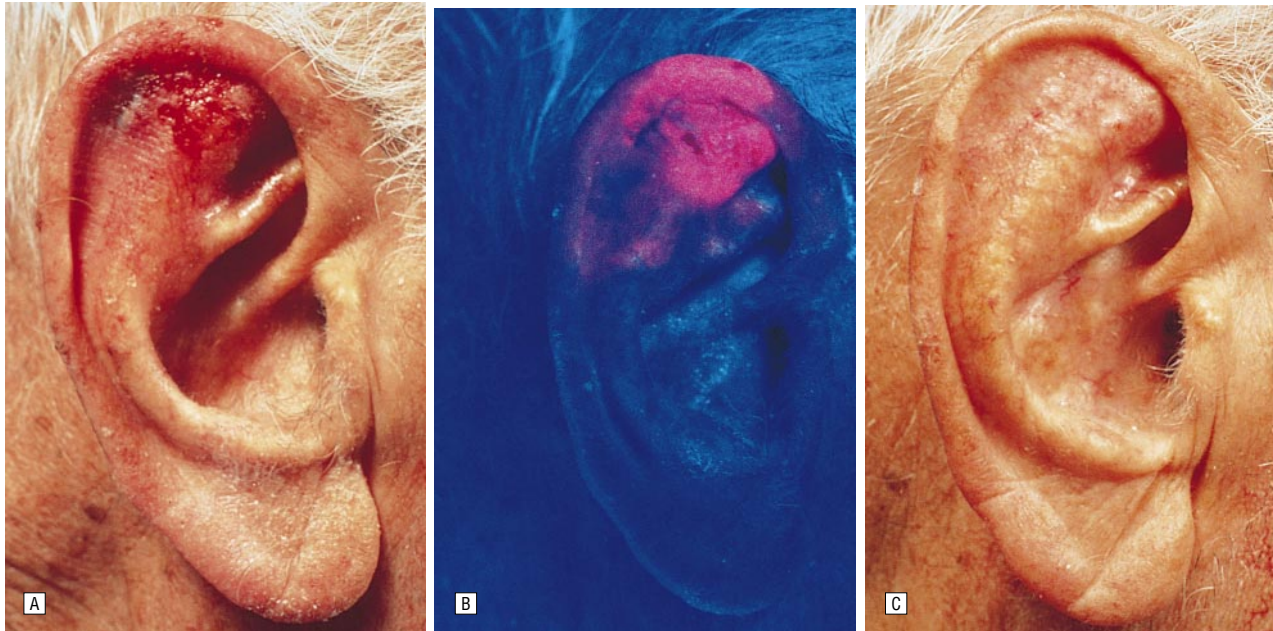


Figure 2. A, Squamous cell carcinoma on the ear helix in a 72-year-old man. B, Photodynamic diagnosis clearly demarcates the extension of the lesion. C, Three photodynamic therapy sessions (20% δ -aminolevulinic acid, 180-J/cm² red light) led to a histologically controlled complete response still maintained at 18 months of follow-up.



Figure 3. A, Basal cell carcinoma in the left supra-auricular area of a 62-year-old man. B, Result after 3 photodynamic therapy sessions (20% δ -aminolevulinic acid, 180-J/cm² red light, 570-750 nm).

diation.^{23,27} Therefore, primary surgical excision remains the treatment of choice in large tumors. However, in difficult locations, pretreatment with PDT and subsequent excision of remaining tumor tissue may improve the cosmetic and functional outcome as demonstrated for a large BCC of the breast.³ Nodular and ulcerated BCCs generally show insufficient response (10%-80%) to topical ALA-PDT, and surgical excision is recommended as the treatment of choice.

Bowen Disease. In several patients, successful treatment of Bowen disease (BD) with porfimer sodium and an argon-PDL was described.²⁸⁻³⁰ Bowen disease also shows a good initial response to PDT with ALA, but long-term results vary considerably. Rates of CR of 90% and 100%^{6,24,28} could not be confirmed in subsequent studies,¹⁹ and our own results suggest a CR in only 30% to 50% (Table 2; **Figure 4**). Even repeated PDT treatments (up to 10) yielded a CR rate of only 50% to 70% (C.F. and T.R., unpublished results).¹⁹ Substituting laser for incoherent light sources, however,

led to improved results of ALA-PDT in BD.^{23,24} Incomplete response of BD may be caused by the elevated epithelial layer with reduced ALA penetration. Therefore, surgical excision of BD should be performed if CR is not achieved after 1 or 2 PDT sessions. Tumor size reduction by PDT pretreatment may facilitate subsequent surgical excision.

Solar Keratoses. Solar keratoses currently represent one of the best indications for PDT in dermatology. In most clinical studies, a CR rate of 80% to 100% was achieved with the use of 20% ALA.^{4,7,19,23} Our data suggest that a 10% ALA concentration is sufficient to obtain high response rates with an incoherent light source at an intensity of 80 to 120 mW/cm². Thus, the burning pain experienced by most patients during irradiation of multiple lesions on the scalp can be substantially reduced. In general, 2 PDT sessions are required to achieve a CR of solar keratoses with an excellent cosmetic result (Table 2, Figure 1).

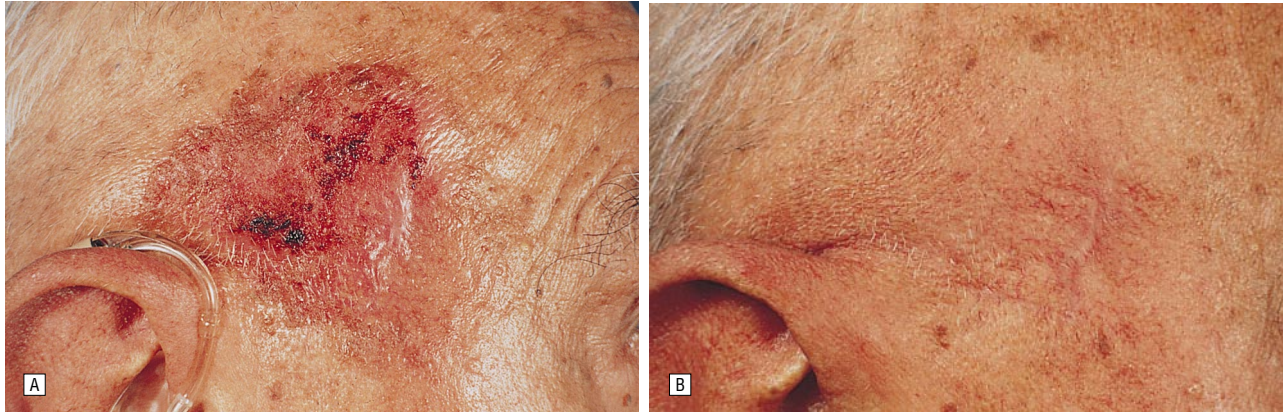


Figure 4. A, Bowen disease with partial transition into Bowen carcinoma. B, One month after complete treatment, there is an excellent cosmetic result. The central tumor was excised and the surrounding Bowen disease was treated by 3 photodynamic therapy cycles (20% δ -aminolevulinic acid, 180 J/cm²).

Squamous Cell Carcinoma. Only a few studies have addressed the use of PDT in squamous cell carcinoma (SCC). With monoaspartyl chlorin e_6 or porphyrins as systemic PSs and argon-PDL, 40% to 100% remission of SCCs could be obtained.²⁷ In topical PDT with ALA, the CR rate was 67% to 92% for superficial SCCs and 0% to 67% for nodular SCCs independent of the light source used.^{4,7,23} We achieved a CR after 3 PDT sessions with 20% ALA and an incoherent light source in 10 of 10 selected lesions with the use of optimum irradiation variables (Table 2; Figure 2). In conclusion, initial stages of SCCs can be effectively treated by topical ALA-PDT, and promising remission rates can be obtained even in nodular SCC.²³

Photodynamic therapy also seems to be a promising modality for treating premalignant epithelial lesions and SCCs of the oral mucosa³¹; genital precancerous stages such as erythroplasia of Queyrat³²; actinic cheilitis³³; and tumors in xeroderma pigmentosum.³⁴

Published results of PDT in epithelial skin tumors should, however, be viewed critically because of methodological shortcomings of many studies. Histological examination demonstrated tumor tissue in a large proportion of tumors despite clinical regression after a single PDT cycle, and tumor recurrence was common after long-term follow-up.²³ Our experiences point in the same direction and also show tumor remnants in the medium and deep dermis covered by normal skin. In conclusion, follow-up periods in most published studies were too short and CR rates based on clinical regression alone are unrealistically high. This lack of topical PDT efficacy in more deeply localized and remaining tumor parts may result from the limited photophysical properties of PDT, the limited permeability for ALA because of covering by normal skin, and the presence of encapsulated tumor cell islands resistant to ALA permeability.^{15,35} Thus, it is not useful to wait for the therapeutic outcome after the first PDT cycle because normal skin will cover possible tumor remnants in deeper tissue layers. In superficial BCCs and superficial SCCs, 1 to 3 PDT sessions are sufficient to induce a CR. In contrast, recurrent or large superficial BCCs respond poorly to additional PDT sessions. Others²³ also reported the necessity of 1 to several treatments grossly related to thickness and pigmentation of the lesions. Epithelial skin tumors of nodular type may require up to 8 treatment sessions. Our pre-

liminary results indicate that performance of several PDT cycles with short intervals (2-7 days) independent of the clinical result after the first treatment is advisable. Fractionation of each PDT session into 2 to 4 irradiation cycles may also increase the effectiveness of treatment.

Malignant Melanoma. So far, there is little information on the efficacy of ALA-PDT in the treatment of primary and metastatic malignant melanoma, and the results are contradictory.^{4,21} The high pigmentation of melanoma tissues may be the limiting factor by inhibiting light penetration.

Cutaneous and Subcutaneous Metastases. Some clinical PDT studies focused on the treatment of breast cancer and other metastases, although with minor benefit (systemic PDT, 4%-75% CR rate^{36,37}; topical ALA-PDT, 0%-83% CR rate^{4,6,7}).

Mycosis Fungoides. Topical ALA application and subsequent exposure to polychromatic or laser light was successfully used to treat plaque-stage cutaneous T-cell lymphoma.²⁹ In another study that used laser light, 2 of 4 lesions were effectively treated.³⁸ However, the apparent clinical cure was not confirmed histologically.³⁹ Further studies on PDT of mycosis fungoides are required to allow final conclusions.

Kaposi Sarcoma. Classic Kaposi sarcoma has been successfully treated, showing early and late CR.²¹ In 5 patients with multiple oral lesions of Kaposi sarcoma related to the acquired immunodeficiency syndrome, therapy with porfimer sodium and an interstitial or surface argon-PDL irradiation induced a regression in approximately 60% of tumors.⁴⁰

Nontumoral Applications of Topical ALA-PDT

Psoriasis. The use of PDT in psoriasis using hematoporphyrin and light was first reported in 1937. Systemic and topical sensitization with hematoporphyrin followed by visible light irradiation resulted in clinical improvement of psoriatic plaques and palmopustular psoriasis.^{41,42} Topical ALA-PDT was speculated to be comparable with anthralin in psoriasis therapy and may be based on the inhibition of inflammatory cytokines. Advan-

tages of this approach would be higher lesion selectivity of the PS compared with psoralen, deeper tissue penetration of red light compared with UV-A, and avoidance of generalized cutaneous photosensitization.⁴³ Since PDT does not covalently bind to DNA, the risk of malignant neoplasm seems lower than with psoralen plus UV-A. On the other hand, tissue distribution of ALA-induced porphyrins is not homogeneous in psoriatic plaques and is not enhanced by occlusive application (C.F. and T.R., unpublished results).^{44,45} Further biochemical studies on the quantitative and qualitative porphyrin accumulation in ALA-treated psoriatic lesions are necessary.

The difficulty in substrate application and insufficient light sources are drawbacks limiting the practicality of PDT, especially in disseminated psoriasis lesions. Further areas of research are topical application of the PS itself in cream form, as exemplified in BCC with tetrasodium-meso-tetraphenylporphyrinsulfonate. Bathing in a PS-containing solution is another interesting procedure. Systemic administration of ALA may result in more homogeneous and selective lesional accumulation of porphyrins in psoriatic lesions, as already shown in BCCs,¹⁵ but pharmacokinetic and toxicity issues are not yet settled. Red light-emitting cabins or high-dose UV-A1 (340-400 nm) may prove superior to presently available lamps for whole-body PDT.

Other Indications. Acne, viral warts, alopecia areata, portwine stains, and hair removal are subject to current clinical investigation.

OPTIMIZATION AND EFFICACY CONTROL OF PDT THERAPY

The main disadvantage of PDT is the lack of histopathologic control. However, alternative methods allow for control of PDT efficacy. Techniques to measure light fluence within tissue, PS concentration, tumor tissue oxygen consumption, and radical generation are being developed to assist PDT treatment.

The clinical demarcation of BCCs and SCCs, particularly in anatomically difficult sites such as the face, is a frequent problem, also because the tumors may extend beyond the clinically apparent margins, especially in actinically damaged skin. In certain body areas, radical surgery is limited by anatomical structures, and the loss of healthy tissue is to be kept low. Histopathologic examination allows delineation of the tumor margins only after their excision. Thus, multiple surgical procedures can become necessary for complete tumor removal.

Photodynamic diagnosis (PDD) with ALA helps to guide tumor therapy. (The term PDD is not actually correct, since reactive oxygen species are not involved in fluorescence diagnosis techniques. However, we keep the name because it has already been widely used in the literature.) In ALA-PDD, porphyrin fluorescence is detected under irradiation with a Wood light (370-405 nm) (Figures 1, B, and 2, B). We investigated the usefulness of ALA-induced porphyrin fluorescence in preoperative demarcation of ill-defined clinical tumor margins and as a control after PDT.^{3,45,46} There was a strong correlation

between clinical extension and fluorescence pattern of the tumors. In addition, all fluorescent areas were proved to be neoplastic by histopathologic examination. The use of ALA-PDD allowed delineation of clinically ill-defined tumors and detection of tumor relapses or new tumors that were not clinically detectable.

PERSPECTIVES OF PDT IN DERMATOLOGY

Photodynamic therapy with ALA is effective in the treatment of solar keratoses, small superficial BCCs, and superficial SCCs. In contrast, PDT is only of minor benefit in the treatment of large superficial BCCs and nodular or pigmented skin tumors. Development of more effective light sources and the use of new promising compounds, including esterified ALA derivatives or second-generation PSs such as porphycenes, may enhance PDT efficacy in the future. Further studies should also focus on the systemic administration of ALA because of reported improved intralesional accumulation of porphyrins. In addition, comparative controlled trials and long-term follow-up studies must be performed to determine whether the clinical efficacy of PDT is comparable with that of other established treatment modalities, such as cryosurgery and curettage-electrodesiccation, especially for thicker skin tumors.

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