Title
Treatment of cutaneous T cell lymphoma, psoriasis and port wine stain birthmarks

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10 Treatment of Cutaneous T-Cell Lymphoma, Psoriasis, and Port Wine Stain Birthmarks

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INTRODUCTION

Photodynamic therapy (PDT) utilizes a photosensitizer and light to generate reactive oxygen species (ROS) which cause tissue damage. PDT involves a photochemical method of injury which is different from the heat-induced effects typically observed during many light–tissue interactions.

PDT has been utilized to treat a wide range of benign, premalignant, and malignant dermatologic disorders. Common uses such as treatment of actinic keratoses and skin cancers are discussed in other chapters. PDT has also been evaluated for treatment of other cutaneous disorders, including cutaneous T-cell lymphoma (CTCL), psoriasis, and port wine stain (PWS) birthmarks (Fig. 10.1).

PDT photosensitizers can be applied topically or delivered systemically (oral or intravenous). Because of ease of use and fewer potential side effects, dermatologic PDT most commonly utilizes topical photosensitizers. In the USA, the only FDA-approved topical photosensitizer is 5-aminolevulinic acid (ALA) (see Fig. 1.1A). During clinical use, nonfluorescent, nonphotodynamically active ALA is applied to the skin where it is transformed into highly fluorescent and photodynamically active protoporphyrin IX (PpIX) via the heme cycle (see Box 1.2). However, in some cases, systemic photosensitizer delivery may offer significant benefits, e.g. in treatment of PWS where such administration offers an opportunity for vascular compartmentalization and selective vascular destruction.

CUTANEOUS T-CELL LYMPHOMA

CTCL is a malignant neoplasm of T lymphocytes, specifically T-helper cells. CTCL presents clinically as patches, plaques, tumors or erythroderma and requires histologic correlation for definitive diagnosis (Fig. 10.2). Prognosis varies with the degree of systemic and cutaneous involvement, and severe disease requires aggressive systemic treatment. However, patients with disease limited to the skin may be candidates for ALA-PDT.

Many treatment options are available for CTCL, including topical corticosteroids, topical nitrogen mustard, retinoids, psoralen in combination with UV irradiation (PUVA), radiation therapy, excision, and CO_2 laser surgery. Each of these therapies has limitations related to adverse effects or efficacy, and as such, alternatives are often sought. Topical ALA-PDT is one option, which may be useful for treatment of localized CTCL. Selective ALA uptake into lesions occurs after application, with subsequent inhibition of malignant transformed T cells. Malignant blood cells may also have an increased ability to convert ALA into PpIX as compared to normal blood cells.

• Patient selection

Topical ALA-PDT may be appropriate for CTCL patients with difficult-to-treat lesions because of localized resistance, location or other health considerations.

• Expected benefits

Complete clinical remission of localized CTCL has been achieved with ALA-PDT, although not for all lesions (Table 10.1). Prolonged remission may occur and has been reported with follow-up as long as 3 years. However, it is also important to note that on occasion, clinical resolution is observed, but biopsy reveals persistent malignant lymphocytic infiltration. This may be most common when lesions appear to clear after one treatment. As such, careful monitoring post-treatment is required.

• Treatment techniques

No standardized protocol exists for treatment of CTCL with PDT. Table 10.1 lists some of the studies which have evaluated different treatment strategies. Twenty percent ALA has been used most commonly. Application time has varied in investigations, but a period of 4–6 h appears to be adequate, especially when the area is occluded (generally with a light-shielding dressing).

Oseroff et al evaluated the effect of light dose and intensity on clinical effectiveness. They found that response increased with fluence (starting at 10 J/cm^2), reaching a plateau at 75–100 J/cm^2. Intensity also affected treatment response, with 150 mW/cm^2 being more effective than lower fluence rates.

Edstrom et al studied the effects of fluence, intensity, and lesional area on treatment tolerance. They started

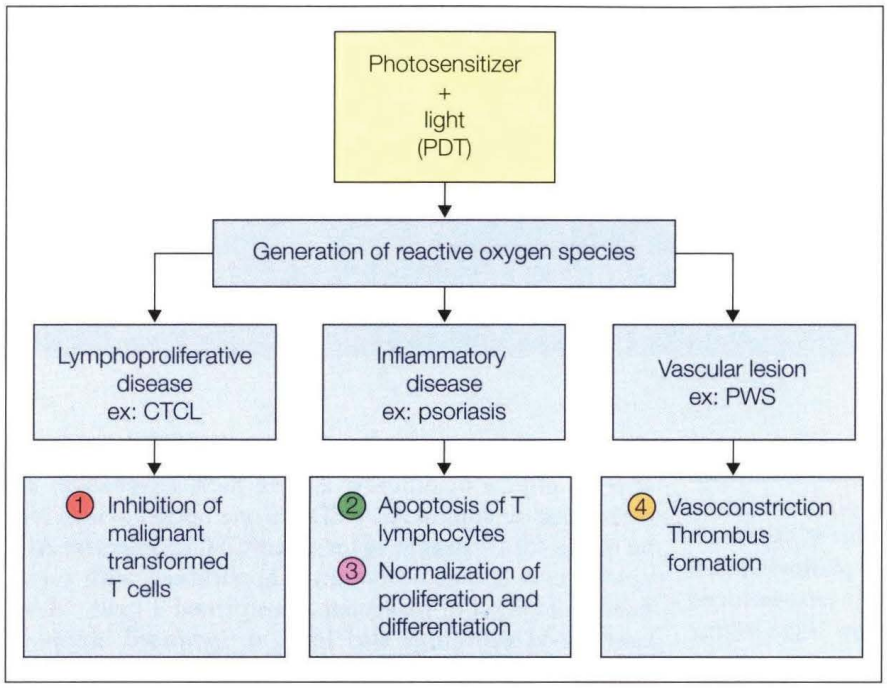

Fig. 10.1 Proposed mechanism for PDT effect in lymphoproliferative, inflammatory, and vascular disorders. 1 = Boehncke et al (1994); 2 = Bissonnette et al (2002); 3 = Fransson & Ros (2005); 4 = Major et al (1997)

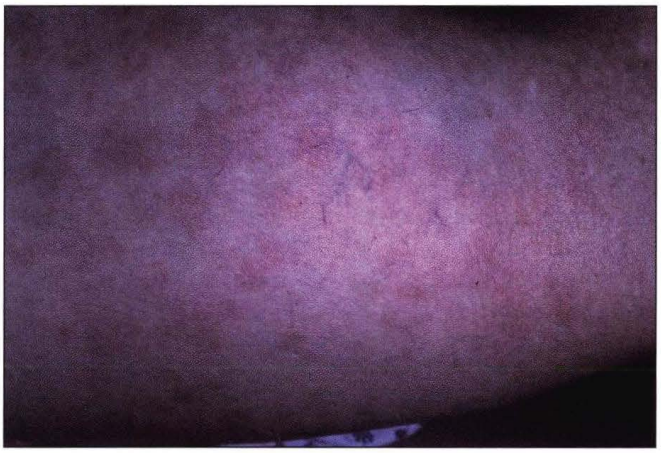

Fig. 10.2 Female with cutaneous T-cell lymphoma on her left leg. Clinical presentation confirmed by biopsy

with a fluence of 180 J/cm^2 but halved this later in their study, secondary to pain. High intensities (200–300 mW/cm^2) were difficult for patients to tolerate, while intensities of 35–125 mW/cm^2 were more comfortable and achieved a good clinical outcome. They also noted that treatment of larger areas resulted in greater pain.

Fractionation may improve results, especially in thick lesions. Orenstein et al used a 30-min irradiation session (580–720 nm, 140 mW/cm^2, 252 J/cm^2) followed by a 1-h dark period and then a second 10–15 min of irradiation (total cumulative dose 340–380 J/cm^2) for 1–4-mm deep tumor stage lesions. Leman et al theorized that fractionation might allow oxygen replenishment and improve the efficiency of the photodynamic process.

Orenstein et al demonstrated the utility of online in vivo fluorescence monitoring as a method to determine optimal light dosing for PDT (Fig. 10.3). For fluorescence detection, they used blue light (400–450 nm, 20 mW/cm^2) delivered by an optical fiber. A CCIR camera was used for imaging and a CCD-based fiberoptic spectrometer (spectral range 570–720 nm, spectral resolution 10 nm) was used for assessment of fluorescence signal intensity. Fluorescence imaging and spectroscopy were performed pretreatment, during treatment, and then 1 h after treatment. Using this imaging technique, re-treatment was considered for lesions for which PpIX fluorescence recurred (most commonly for thicker lesions).

Persistent lesions in difficult-to-treat anatomic locations may provide ideal opportunities for the use of ALA-PDT. Wang et al evaluated the use of ALA-PDT for resistant periocular T-cell lymphoma. One patient had three lesions on the medial canthus and lower eyelids bilaterally and had failed nine cycles of chemotherapy. The eye to be treated was covered with a specially designed intraorbital lead shield. Lesion surface was gently scraped with a scalpel to improve ALA penetration, although significant curetting was not performed (minimizing scarring and limiting discomfort). ALA powder (Porphyrin Products, Logan, Utah) was dissolved in neutral eye ointment (Emulgon®) to achieve a concentration of 20% ALA. Ointment was applied to lesions and a 5-mm margin and covered with a thin adhesive plastic pad (Tegaderm®, 3M, UK). A complete clinical response (CCR) was achieved after three treatments with no recurrence at 33 months. Cosmetic result was excellent, with no scarring.

Coors et al evaluated the use of topical ALA-PDT for difficult-to-treat CTCL lesions resistant to other

Table 10.1 Summary of studies evaluating treatment of cutaneous T-cell lymphoma with topical ALA-PDT

Reference	No. of sites	Application time (h)	Wavelength (nm)	Intensity (mW/cm^2)	Fluence (J/cm^2)	No. of Rx	Lesion type	Response	Recurrence
Coors & von den Driesch (2004)	7	6	Visible light	60–160	72–144	1–7	5 plaque 2 tumor	CCR all Lesions	None at 14–18 months
Edstrom et al (2001)	12	5–18	600–730	35–300	80–180	2–11	10 plaque 2 tumor	7/10 plaque: CCR 2/10 plaque: Regression 1/10 plaque: No response 2/2 tumor: No response	None in lesions with CCR after 4–19 months
Leman et al (2002)	2	6–24	630	48	100	4	Plaque	CCR all lesions	None at 12 months
Orenstein et al (2000)	6	16	580–720	140	170 patch 380 tumor	1	1 patch 5 tumor	CCR all lesions	None at 24 months
Oseroff et al (1996)	80	Overnight	630	30–150	10–200	1	Not specified	Varied with fluence and intensity	Not reported
Paech et al (2002)	2	4	580–740	Not reported	180	2	Plaque	CCR in all lesions	Not reported
Wang et al (1999)	3	4–6	635	<110	60	3	Periocular	CCR all lesions	None at 33 months

CCR = complete clinical response

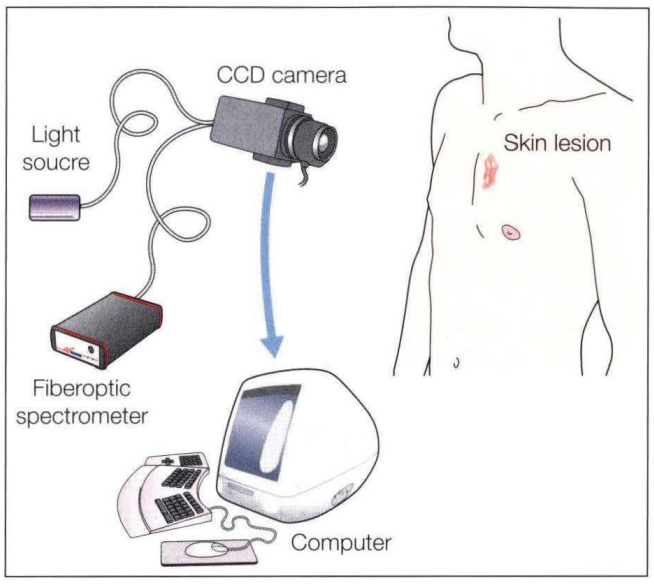

Fig. 10.3 Schematic diagram of fluorescence monitoring during ALA-PDT treatment

therapies. They achieved complete resolution of seven previously resistant lesions after treating them with 20% ALA, under occlusion for 6 h, followed by visible light irradiation.

An HIV-infected patient with CTCL was successfully treated with ALA-PDT by Paech et al. ALA ointment was applied under occlusion to plaques for 4 h, followed by light exposure (580–740 nm) generated by a PDT 1200 irradiation source (Waldmann Medizintechnik, Germany), achieving a dose of 180 J/cm^2. Complete remission was achieved after two cycles of PDT, spaced 4 weeks apart.

• Side effects and complications

Moderate-to-severe discomfort is common during topical PDT treatment of CTCL. Measures to ameliorate some discomfort include the use of intralesional anesthetics, water spray during treatment, liquid nitrogen sprayed repeatedly in the air about 10 cm above the treated lesion, and cold air epidermal cooling. The post-treatment period includes erythema, edema, and epidermal sloughing. Erosion and ulceration may occur. Lesions generally heal with a good cosmetic outcome, although pigmentary changes and scarring can result. It is important to note that light protection practices are important for 48 h following topical ALA-PDT to prevent phototoxicity at treated sites.

• Summary

PDT is an option for treatment of CTCL, although further work is required to optimize treatment parameters. Patients with difficult-to-treat lesions because of localized resistance, location or other health considerations, may be optimal candidates. Careful monitoring for systemic disease or local recurrence is important for all patients with CTCL and must be included in any treatment strategy.

PSORIASIS

Psoriasis is a common inflammatory disorder affecting up to 2% of the population. Characterized by erythematous plaques with silvery white scales, mostly over extensor surfaces, psoriasis is a disease that inflicts significant psychosocial morbidity on those affected.

There are many topical treatments available for psoriasis, including vitamin D derivatives, steroids, and retinoids. Moderate-to-severe psoriasis can be treated using systemic medications such as oral retinoids, methotrexate, cyclosporine, biologic agents or light therapy. Despite these many options, some patients do not achieve complete, long-term control of their psoriasis, or experience unacceptable adverse effects. As such, alternative treatment options are sought.

PDT may offer a treatment alternative for patients with resistant psoriasis (Fig. 10.4). Topical and orally administered ALA has been shown to be taken up selectively into psoriasis plaques and converted to PpIX. Bissonnette et al demonstrated apoptosis in T lymphocytes of some psoriatic plaques after PDT following oral administration of ALA. Fransson and Ros noted normalization of proliferation and differentiation markers, including cytokeratin 16 and filaggrin, in psoriatic plaques after two to five treatments with ALA-PDT. Dermal CD4(+) and CD8(+) T cells were also decreased.

• Patient selection

Optimal candidates are those patients who do not require or want systemic therapies and have localized psoriatic plaques that have been resistant to topical medications.

• Expected benefits

In some patients, rapid control of resistant plaques can be achieved. Prolonged remission may be possible but, as discussed below, treatment strategies will need to be optimized to achieve this on a consistent basis.

• Treatment techniques

Similar to CTCL, a range of strategies has been utilized for ALA-PDT psoriasis treatment (Table 10.2) and the best protocol has yet to be established.

The thick hyperkeratotic scale of psoriatic plaques is a barrier to penetration of topically applied ALA. Therefore, antikeratolytic measures prior to ALA application may be useful, provided these are done cautiously to minimize irritation.

Weinstein et al evaluated topical ALA-PDT for psoriasis utilizing differing ALA concentrations (2%, 10%, and 20%) in combination with UVA light (15 mW/cm^2, 2.5–

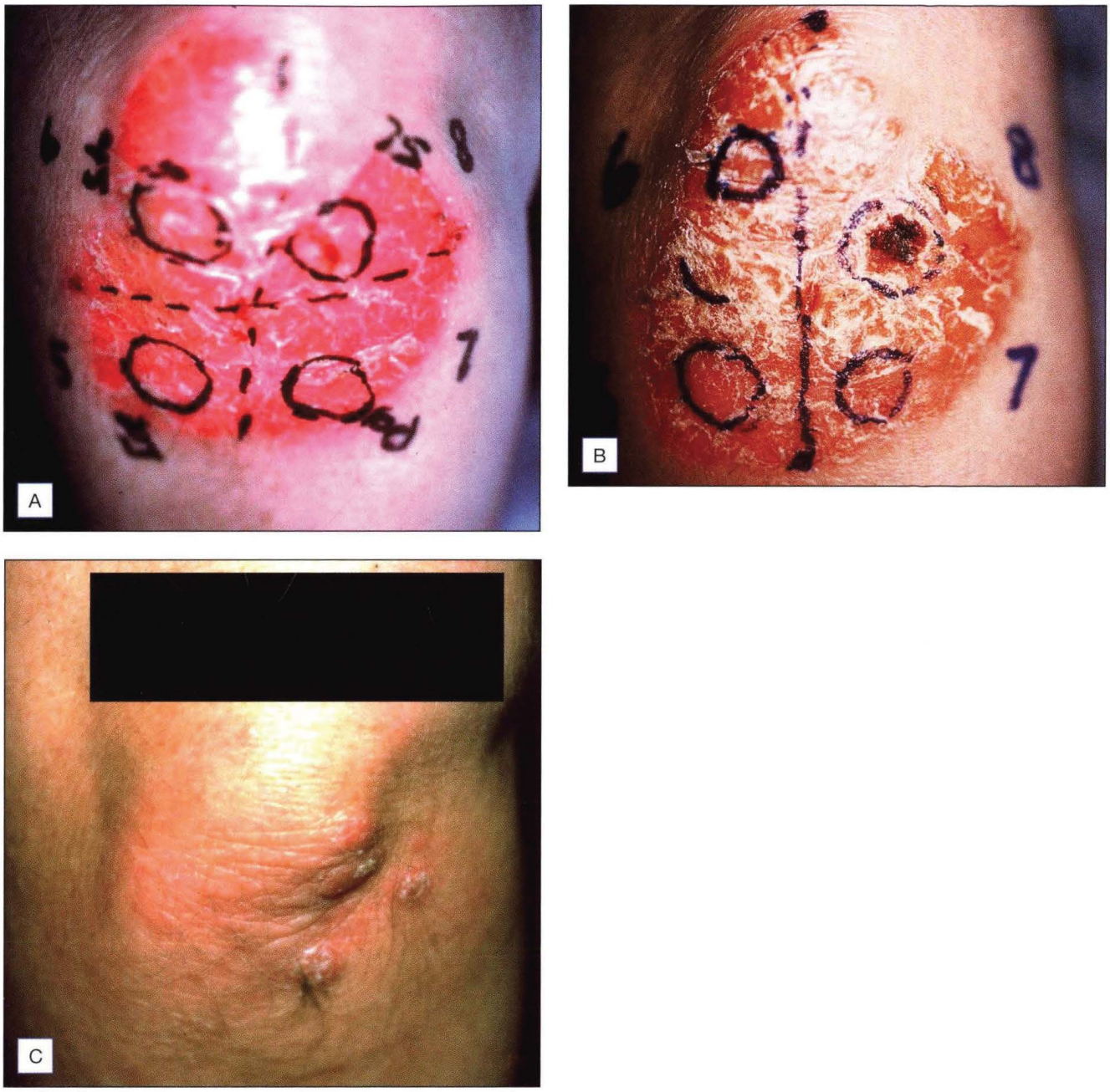

Fig. 10.4 Psoriasis plaque (**A**) before, (**B**) 2-weeks post- and (**C**) 3 months post-PDT treatment (Courtesy of J.S. Nelson, MD, PhD)

3 J/cm^2). Best results were noted with 10% and 20% ALA, achieving greater than 50% improvement after four weekly treatments.

Fritsch et al studied varying application times of topical ALA and concluded that 6 h of application appears to be optimal in terms of the highest porphyrin accumulation in psoriatic lesions; however, they and others found variable PpIX accumulation in psoriatic plaques.

Robinson et al proposed that regimens with multiple planned treatments may achieve greater therapeutic success. They evaluated 19 sites after application of topical 20% ALA for 4 h followed by broadband visible radiation with a modified slide projector (15 mW/cm^2, 2–8 J/cm^2), for up to 12 treatments, one to three times a week. Eight of the 10 patients improved, with four of the 19 sites resolving completely.

Rapid clinical clearance of psoriatic plaques was reported by Collins et al. They treated 36 trunk and extremity sites with 20% topical ALA applied for 4 h and irradiated with 400–650-nm light from a modified slide projector, at 10–40 mW/cm^2, for a total fluence of 2–16 J/cm^2. When evaluated 11–17 days after a single

Table 10.2 Summary of studies evaluating treatment of psoriasis with ALA-PDT

Reference	No. of sites	ALA administration	Wavelength (nm)	Intensity (mW/cm^2)	Fluence (J/cm^2)	No. of Rx	Response	Recurrence
Bissonnette et al (2002)	180	1, 3, 6 h Oral	417	9–11	1–20	1	0–42%	Not reported
Collins et al (1997)	36	4 h Topical	400–650	10–40	2–16	1	10 lesions clear 4 30–50% reduction 22 no change	5–14 days later
Kim et al (2005)	4	5 h Topical	632	30	15	11	Near complete clearance	Not reported
Radakovic-Fijan et al (2005)	29	Application time not reported Topical	600–740	Not reported	5, 10, 20	Up to 12	Psoriasis severity reduction of: 59% ($20 J/cm^2$) 49% ($10 J/cm^2$) 46% ($5 J/cm^2$)	Not reported
Robinson et al (1999)	19	4 h Topical	Broadband visible	15	2–8	7–12	4 lesions clear, 10 improved, 5 no change	Not reported
Weinstein et al (1994)	84	3 h Topical	Ultraviolet A	15	2.5–3	1–4	Variable Improvement	Not reported

treatment, seven of the 22 test subjects showed improvement, with 10 of the 36 treated lesions clearing completely and four reducing by up to 50%. Lesions began to recur within 2 weeks.

Radakovic-Fijan et al pre-treated 29 patients with a keratolytic consisting of 10% salicylic acid in white petroleum for up to 2 weeks. This was followed by application of 1% ALA (for an unspecified period of time) and irradiation with a filtered halide lamp (Waldmann PDT 1200, 600–740 nm) for a light dose of 5, 10 or 20 J/cm^2. Treatments were performed twice weekly for a total of 12 sessions or until clearance. Psoriasis severity index (PSI) showed a final reduction of 59% in the group treated with 20 J/cm^2, as compared to 49% and 46% improvement achieved with light doses of 10 J/cm^2 and 5 J/cm^2, respectively. The difference in clinical efficacy between 20 J/cm^2 and 10 or 5 J/cm^2 was statistically significant ($P = 0.003$; $P = 0.02$).

Oral administration of ALA may offer advantages over topical application for ALA-PDT treatment of plaque psoriasis. Bissonnette et al had patients ingest ALA (5, 10 or 15 mg) and then after a period of 1–6 h exposed psoriatic plaques to a blue fluorescent lamp at 9–11 mW/cm^2 using fluences up to 20 J/cm^2. PpIX fluorescence increased rapidly and significantly in psoriatic plaques, reaching a maximum at 2–3 h. Maximal improvement (42% diminution in PSI at 28 days as compared to baseline) was seen in patients who received 10 or 15 mg of ALA followed after 3 h by 10 J/cm^2 of blue light.

While most studies have evaluated treatment of plaque psoriasis, PDT has also been used for palmoplantar pustular psoriasis. In a case report by Kim et al, a patient with pustular psoriasis resistant to topical steroids, acitretin, and methotrexate had 20% ALA applied topically for 5 h under occlusion followed by irradiation with a 632-nm diode laser (30 mW/cm^2, 15 J/cm^2). The lesion was almost completely cleared after 11 weekly treatments for a total cumulative dose of 165 J/cm^2.

• Side effects and complications

Patients undergoing topical ALA-PDT for psoriasis frequently experience pain, burning, and itching, during and up to 72 h post-treatment. Severity of symptoms ranges from mild to severe. Erythema, mild edema, and occasionally erosions may occur post-treatment, especially when

higher light doses are used. Post-inflammatory hyperpigmentation often occurs with plaque resolution, although scarring is generally not reported.

While administration of oral ALA has been associated with nausea, vomiting, and hypotension, the 5-, 10- or 15-mg doses used by Bissonnette et al resulted in only one of 12 patients reporting mild nausea. One patient (who received 15 mg) reported a mild burning sensation during light exposure. Asymptomatic erythema and edema lasting 3 days also occurred.

Photosensitivity results post oral or topical administration of ALA, making photoprotection necessary.

• Summary

Pain and unpredictable response are major limitations of topical ALA-PDT treatment of psoriasis. Oral ALA-PDT may be an alternative and facilitates treatment of large body surface areas. Post-treatment photosensitivity is an issue, but may be tolerated if optimization of treatment strategies results in consistent and rapid improvement of resistant plaques. Further research is required to evaluate the psoriatic treatment potential of ALA-PDT and to determine the place of this modality in the psoriatic treatment armamentarium.

PORT WINE STAIN BIRTHMARKS

PWS birthmarks are congenital, vascular malformations of the skin found in 0.3% of the population. While they may be located anywhere on the body, they are most commonly found on the face and can have serious psychological consequences. Additionally, these lesions may be associated with medical complications, including glaucoma, hypertrophy, or local bleeding.

The pulsed-dye laser (PDL) is the standard of care for treatment of PWS but achieves complete clearance in less than 20% of lesions. Therapeutic efficacy of PDL for PWS is affected by a variety of factors, including energy limitations secondary to risk of thermally induced epidermal injury and the inability of PDL to destroy microvessels (diameter < 20 μm).

PDT has been evaluated for PWS birthmarks and may offer an alternative treatment option. PDT uses a continuous wave (CW) light source to provide photons at a desired wavelength, driving photochemical reactions without heat generation. Milliwatt light exposure used during PDT does not cause the epidermal thermal injury produced by high peak power PDL. Further, PDT can destroy vessels of all sizes that contain the photosensitizer, including microvessels spared by PDL.

PWS treatment requires careful design of PDT to achieve selective destruction of PWS vessels without full thickness vascular elimination, which is likely to result in skin necrosis. While topical ALA-PDT has been considered by some for the treatment of PWS and other vascular lesions, this approach is unlikely to result in significant success, due to an inability to achieve vascular compartmentalization. PDT with systemically administered photosensitizers has been evaluated in PWS patients.

• Patient selection

Use of PDT for PWS is currently investigational but may one day offer an option for those with resistant PWS.

• Treatment techniques

Early evaluations from China and the USA (JS Nelson, personal communication) using blue and red light,

Table 10.3 Summary of studies evaluating treatment of PWS birthmarks with PDT

Reference	No. of sites	Photosensitizer	Wavelength (nm)	Intensity (mW/cm^2)	Fluence (J/cm^2)	No. of Rx	Response*
Evans & Kurwa (2004)	8	30 mg/kg Oral ALA	585	N/A	6.5	3	No significant difference between PDL alone vs. PDL + ALA
Lin et al (1997)	118	4–7 mg/kg Intravenous PSD-007	578	40–90	NR	1	27.1% excellent results 46.6% good results 24.6% fair results 1.7% poor results
Tournas et al (2006)	8	Verteporfin 6 mg/m^2	576	100	Up to 75	1	Variable

respectively, resulted in a relatively high incidence of scarring and prolonged photosensitivity (30 days or more).

Lin et al (Table 10.3) evaluated 118 PWS patients who received a purified mixture of six kinds of porphyrin molecules (PsD-007; intravenous 4–7 mg/kg) followed within 30 min by exposure to 578-nm light (40–90 mW/cm^2). Up to 70 cm^2 were treated per session which took 1–2 h. After one treatment, 27.1% of patients had excellent results, 46.6% had good results, 24.6% had fair results, and 1.7% had poor results. Patients were photosensitive for 2 weeks. No hypertrophic scarring or permanent dyspigmentation was reported.

Evans and Kurwa used orally administered ALA (30 mg/kg) and PDT for PWS treatment. Each lesion was divided into three equal areas: (1) PDL alone (1.5 ms; 6.5 J/cm^2); (2) PDL 1 h after administration of ALA; or (3) PDL 2 h after administration of ALA. Patients received three treatments at 4-weekly intervals but no significant difference was found between the three areas. It is possible that the relatively short pulse duration of the PDL (1.5 ms) did not allow adequate generation of cytotoxic species to achieve prolonged vascular effect. Moreover, currently available forms of ALA are not vascular specific, making it difficult to find optimal treatment parameters which allow selective and significant vascular destruction without epidermal injury.

We have proposed combining PDT-induced photochemical and PDL-induced photothermal injuries to achieve a synergistic effect. Initial subtherapeutic PDT exposure makes PWS blood vessel walls, especially smaller vessels (potentially not affected by PDL alone), more vulnerable to subsequent photothermal damage. Subsequent PDL irradiation heats vessels compromised by PDT. Careful parameter selection for both PDT and PDL confine therapeutic effects to the upper 1000 μm of the dermis, containing ectatic PWS venules, while reducing the risk of possible skin infarction which could result from destruction of the lower vascular plexus.

In our protocol, benzoporphyrin derivative monoacid ring A (BPD; Visudyne, QLT, Inc, Vancouver, Canada) is administered intravenously at a dose of 6 mg/m^2, over a 10-min infusion period. Starting 15 min after the infusion onset, PDT irradiation is performed using a CW argon pumped dye laser (rhodamine 560; λ = 576 nm) and a power density of 100 mW/cm^2. This is followed immediately by PDL (585 nm; pulse duration 1.5 ms; 8 J/cm^2). This approach demonstrated significant promise in early animal studies in which PDT + PDL resulted in a statistically greater reduction in vascular perfusion (56%) as compared to either PDT or PDL alone.

Preliminary clinical studies using the PDT + PDL approach were recently reported. In order to increase safety of the study, PDT light dose was initiated at the very low light dose of 15 J/cm^2 and increased by 15 J/cm^2 over the course of the study, to a maximum of 75 J/cm^2. No significant adverse effects related to treatment were noted. PDT + PDL sites demonstrated increased purpura as compared to the PDL-alone test sites (Fig. 10.5). Purpura is a sign of vascular damage and increased purpura has been associated with improved PWS response. Two patients demonstrated improved blanching in the PDT + PDL sites (Fig. 10.6). It is important to note that preliminary animal experiments were conducted using a CW light dosage of 96 J/cm^2. Based on these results, greater effect can be expected to be seen in the PDT and PDT + PDL sites as CW light dosage is increased.

• Side effects and complications

PDT for treatment of vascular lesions must be approached cautiously as there is potential for total vascular destruction and subsequent scarring. Careful design of protocols may help avoid this potential pitfall. Post-treatment patients are photosensitive for variable duration depending on the photosensitizer and must be counseled about photoprotective measures.

• Summary

Further research is required but PDT alone or in combination with PDL may offer an approach for resistant cutaneous vascular lesions.

CONCLUSION

PDT has been used as an alternative treatment option for CTCL and psoriasis and is under investigation for PWS birthmarks. PDT is not first-line therapy for these indications but may offer a treatment option for those who have failed conventional treatments.

ACKNOWLEDGMENT

We would like to thank Dr Ronald J. Barr for his contribution to this chapter.

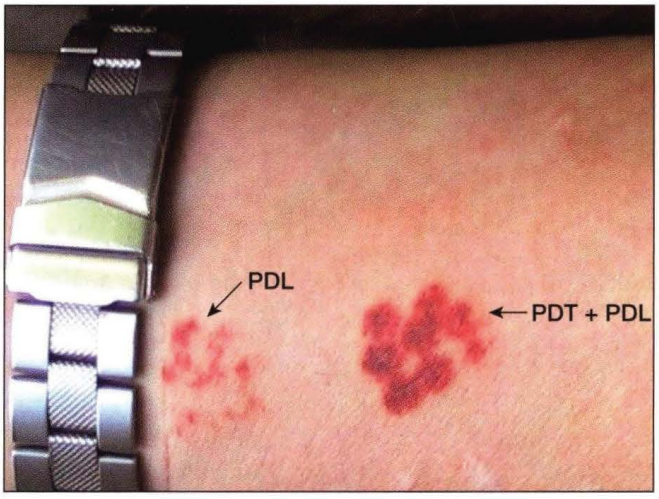

Fig. 10.5 Increased post-treatment purpura noted after PDT + PDL as compared to PDL alone utilizing a CW light dose of 45 J/cm^2 for the PDT spot.

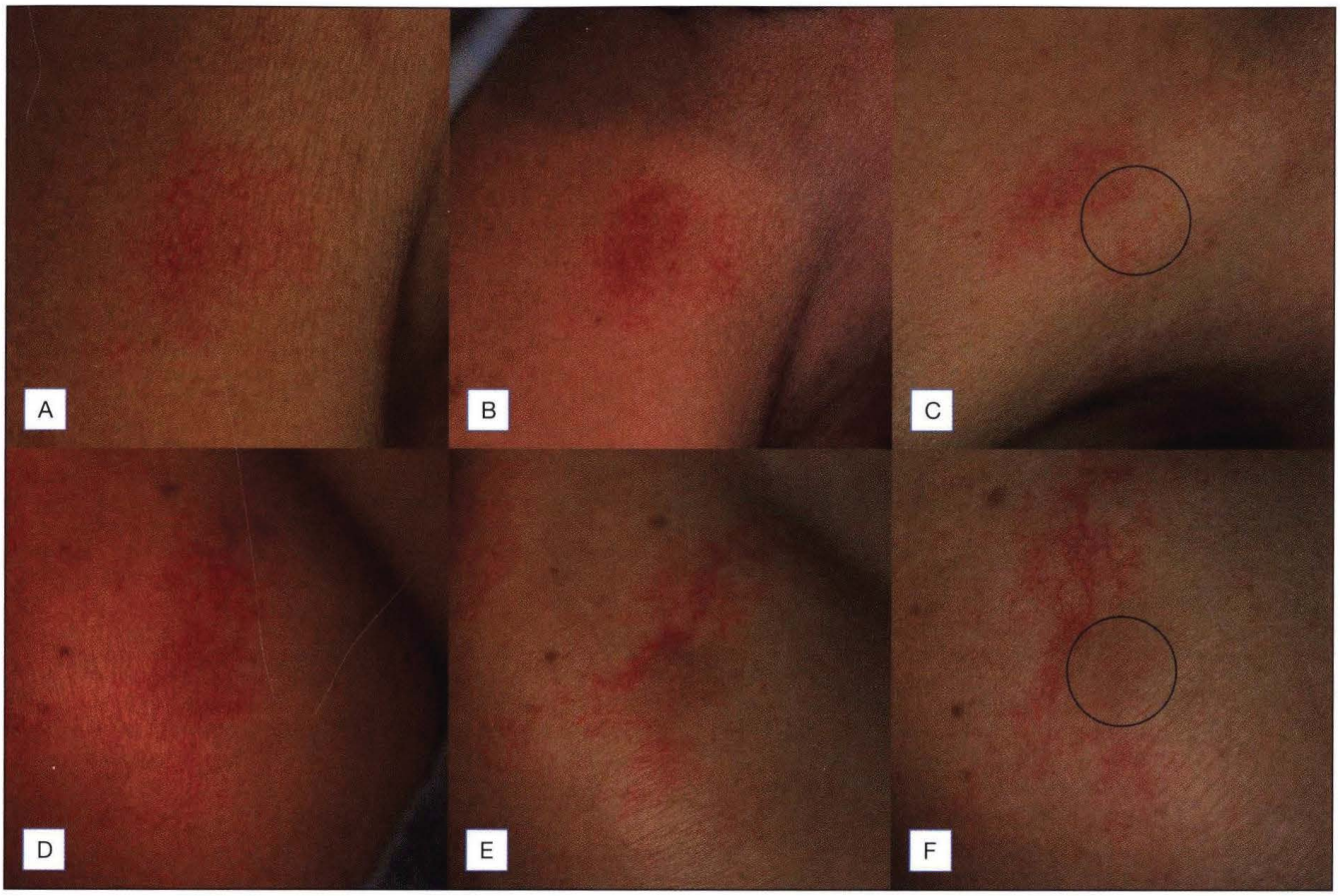

Fig. 10.6 PDL spot (**A**) before, (**B**) 4 weeks post, and (**C**) 8 weeks post intervention. PDT (45 J/cm^2) + PDL spot (**D**) before; (**E**) 4 weeks post, and (**F**) 8 weeks post intervention. Treatment area is outlined in **C** and **F**. Note improved PWS blanching in the PDT + PDL test spot as compared to PDL alone. No PWS blanching was noted in the control or PDT spots. Mild hyperpigmentation is noted in the PDT + PDL test

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Procedures in Cosmetic Dermatology

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Second edition

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Four years ago we began a project to produce 'Procedures in Cosmetic Dermatology', a series of high quality, and practical, up-to-date, illustrated manuals on procedures in cosmetic dermatology. Our plan was to provide dermatologists and dermatologic surgeons with detailed books accompanied by instructional DVD's containing all the information they needed to master most, if not all of the leading edge cosmetic dermatology techniques. Thanks to the efforts of our superb book editors, chapter authors, and the tireless and extraordinary publishing staff at Elsevier, the series has been more successful than any of us could have hoped. Over the past 3 years, thirteen volumes have been introduced, which have been purchased by thousands of physicians all over the world. Originally published in English, many of the texts have been translated into different languages including Italian, French, Spanish, Chinese, Polish, Korean, Portuguese, and Russian.

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