EURO-PDT. 3rd Meeting of the European Society for Photodynamic Therapy in Dermatology, Regensburg, Germany, December 5–7, 2002

Michael Heidenheim
Division of Dermatology, Department of Medicine, Roskilde Hospital, Denmark.
E-mail: heidenheim@dadlnet.dk

Photodynamic therapy (PDT) is a treatment modality using a photosensitiser, light and oxygen to cause photochemically induced selective cell death. The use of topical PDT in dermatology has expanded significantly and is now a treatment option for a wide range of skin diseases. The fundamental processes behind PDT were presented at the 3rd Euro-PDT meeting held in Regensburg Germany on December 5–7. 2002, where current and potential applications of PDT and photodynamic diagnosis (PDD) were discussed.

How PDT works

PDT causes cell death by necrosis and/or apoptosis. The efficacy of PDT involves direct cell killing, vascular damage, inflammation, and immune host response. PDT action requires the presence and interaction of 3 components: a photosensitiser, light and oxygen. An exact understanding about the mechanisms of cellular damage is still incomplete. The first step of PDT is to bring a photosensitising molecule to the tumour as selectively as possible.

Panorama of the historical center of Regensburg

Tumour selectivity is based on exogenously administered photosensitising molecules (porphyrins, chlorines, phthalocyanins, etc) or on photosensitisers produced endogenously by applications of precursors, such as 5-laevulinic acid (5-ALA) or its ester derivatives. In itself 5-ALA is not a photosensitising drug, but administration of exogenous 5-ALA induces the build-up of the natural endogenous photosensitiser protoporphyrin IX (PpIX). Cells treated with 5-ALA and derivates accumulate PpIX which, through the formation of singlet oxygen ($^1O_2$) (ROS=Reactive Oxygen Species), causes vital damage to several cellular components, including the mitochondria, endoplasmic reticulum and plasma membrane. The accumulation of PpIX is highly increased in rapidly proliferating cells. The lesions are exposed to light at 630–635 nm 3 to 6 h after 5-ALA application. However, photodynamically active products are also generated at wavelengths beyond the activation spectrum of PpIX, indicating that broadband illumination may be the most effective.

Most photosensitisers are lipophilic and accumulate in membrane structures. Thus, damage to the plasma membrane is of great significance. Furthermore, mitochondrial damage and destruction of microtubuli imply that the cells accumulate in mitosis after PDT, and may subsequently be inactivated. Examples have been reported of less occurrence of metastasis after PDT of the primary tumour than after surgical removal. This may be due to immunological effects. The photosensitisers are primarily localised outside the cell nucleus and since ROS has a short lifetime and a short radius of action, DNA will not be significantly damaged. Therefore, most t-PDT procedures have very low mutagenic and carcinogenic potential. Many photosensitisers are photolabile and degrade during PDT. This may reduce their potential effect, and may consequently result in protection of normal tissue.

Methylesters of 5-ALA are believed to be generally more efficient and selective in inducing porphyrin accumulation in malignant tissue than 5-ALA itself. This may be due to an enhanced transcellular penetration.

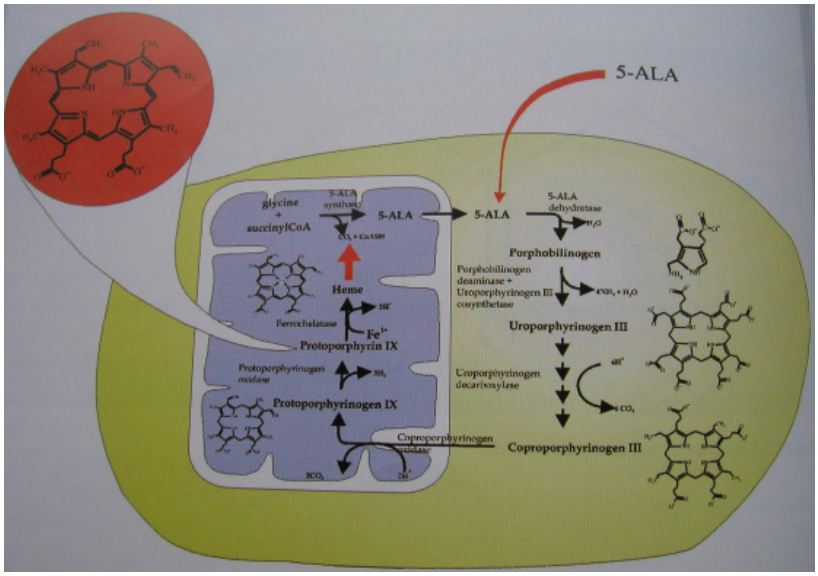
Oncological indications for PDT – present status and future developments

Actinic keratoses

The conversion rate of actinic keratosis (AK) to squamous cell carcinoma (SCC) appears to be in the range of 0.25 to 1% per year. It is estimated that 60% of SCCs of the skin probably arise from AK. In patients who have numerous AK, monotherapy with PDT seems useful and has been shown to be superior to cryotherapy and equivalent to topical 5-fluorouracil in clearing non-hyperkeratotic actinic keratoses. PDT may also achieve a better cosmetic outcome than conventional therapy (H. Hönigsmann, Austria). A complete response rate of 90% for PDT for AK has been reported in several studies. PDT is mostly given as a single irradiation, repeated after a healing phase of 1–2 weeks. Ineffective penetration of 5-ALA, resulting in an insufficient level of PpIX, may be a problem when treating thick hyperkeratotic lesions. In such cases, keratolysis prior to treatment and multiple treatments are necessary.

Bowen's disease

Bowen's disease (BD) is highly responsive to systemic PDT but the clinical outcome varies, with long-term cure rates from 50% to 100% (C. Morton, UK). The differences may be due to the use of different light sources. Current evidence indicates t-PDT to be superior to topical 5-fluorouracil, and equivalent to cryotherapy in BD, with fewer adverse reactions such as ulceration and infection. A recent British Photodermatology Group workshop has published a study on the use of PDT for non-melanoma skin cancers including the widespread forms of BD, large BD patches, and lesions in anatomically difficult areas, where invasive methods were less applicable because of tissue destruction (Guidelines for topical photodynamic therapy (Morton CA, et al. Br J Dermatol 2002;146:552–567)).



The heme synthetic pathway occurs partly in the mitochondria and partly in the cytosol. The red arrow indicates the feedback inhibition of 5-ALA synthase by heme.

Basal cell carcinoma

Basal cell carcinoma (BCC) represents the most common cutaneous malignancy treated by PDT which is safe and effective for the eradication of superficial BCCs with cure rates ranging from 79% to 100% (A-M. Wennberg, Sweden). Topical PDT is most suitable for the treatment of multiple and extensive tumours when surgery would lead to cosmetic or functional impairment. Similarly, PDT is used as an alternative for patients who are unable to undergo surgery for medical reasons or who have previously been treated with radiation therapy. A variable uptake of 5-ALA and/or its insufficient conversion to PpIX in the tumour cells may be responsible for some reports of therapeutic ineffectiveness. The inverse correlation of tumour thickness with the response rate of superficial BCCs to topical ALA-PDT has been shown. Thin lesions (<1 mm) responded completely after the application of ALA for 4 h and coherent light, whereas thicker BCCs (1–2 mm and >2 mm) showed only insignificant response.

Squamous cell carcinoma and lymphoma

These types of skin cancer have been found to be susceptible to PDT in

preliminary studies (P. Calzavara-Pinton, Italy). A majority of patients with SCC receiving PDT have been treated with topical 20% ALA and incoherent light sources at different doses (30 to 540 J/cm^2). In situ SCCs and early invasive tumours show cure rates between 40% and 100%, including data from repeated PDT sessions. Patients with SCC have achieved complete remission after 3–6 sessions of ALA-PDT. Recurrence rates of 22% in follows-up 1–3 years after the therapy have been reported, but tumours are described as responsive to continuous therapy.

Therapeutic options for cutaneous T–cell lymphoma (CTCL) include topical steroids, topical chemotherapy and phototherapy. Patients with limited disease that are unresponsive to these therapies present a particular challenge, where ALA-PDT may be a useful addition to the therapeutic options for CTCL. A successful treatment of a patient with two plaques of CTCL using 5-ALA-PDT applied 6–24 h prior to illumination with 100 J/cm^2 red light repeated on four occasions has shown clinical and histological clearance. Further studies however are required to define optimal treatment protocols.

Non-Oncological Indications for PDT

Experience of the modality in other skin diseases remains limited.

Psoriasis

Clinical data suggest that PDT may have antipsoriatic potential (A. Tanew, Austria). Although PDT improves psoriasis, the post-treatment hyperpigmentation as well as inconsistent clinical responses despite repeated PDT sessions have limited the development of this treatment approach for psoriasis. At present, the treatment of psoriasis with PDT remains an experimental modality.

Warts

The efficacy of topical ALA-PDT in the treatment of recalcitrant foot and hand warts has been shown in a placebo-controlled, randomised, double-blind trial (I-M Stender, F Olivarius, Denmark). The inactivation of viral particles without host cell death implicates a direct antiviral effect of PDT additional to the destruction of infected keratinocytes. Warts demonstrate a selective accumulation of ALA-induced PpIX compared with surrounding normal skin. However the intensity of ALA-induced PpIX cannot be directly related to the cure rate. Severe and unbearable pain was induced by ALA-PDT in about one fifth of the ALA-PDT treated warts. There was no relation between pain intensity, PpIX intensity and the relative wart area reduction.

Case reports in PDT

Hair disorders and acne

The application of ALA leads to accumulation of PpIX in hair follicles and sebaceous glands, suggesting the potential use of PDT for disorders originating from these skin adnexa. The frequent incidence of hypertrichosis in patients with porphyria cutanea has prompted experimental PDT of alopecia areata.

Alopecia areata was treated 3 times weekly with topical PDT and a metal halide lamp filtered to produce long-wave UVA. In 2 patients, coarse terminal hair was present by the third to fourth month of therapy. In acne, significant clearance and improvement were achieved but side effects were frequent: erythema, pain, stinging, oedema, blistering and transient post-therapeutic hyperpigmentation.

Morphea

More than 25 treatment series of topical ALA-PDT were required (5-ALA for 6 h, irradiation PDT 1200 with 40 mW and 10-20 J/2nd week) for clinical effect. Clinical skin score by palpation of skin hardness (VAS scale) and use of Durameter score showed a 50% reduction in skin hardness (S. Karrer, Germany).

Similar effect from PDT has been shown in the treatment of keloids, hypertrophic scars, systemic scleroderma and sclerotic graft-versus-host reaction.

Lichen sclerosus et atrophicus

A marked reduction of pruritus in 12 patients, with a 6-month follow-up after repeated treatment with 20% 5-ALA 6 h irradition with Ar-dyelaser 3 x /2 weeks.

Cutaneous sarcoidosis

Complete remission was achieved in a 67-year-old female patient with a history of recalcitrant cutaneous sarcoidosis for >17 years 3% ALA 4 h 2 x /week for 3 months.

Lichen ruber

Complete remission after 4 weeks. 20% ALA 2 x /2 weeks.

Side effects

A major problem with PDT is pain management (B. Algermissen, Germany). The side effects during ALA-PDT include burning, stinging and pain. Shortly after PDT, initiation of erythema, oedema, burning, pain and photosensitisation occurs. Erythema, scaling and folliculitis have been described as late side effects.

There is a large variation in pain intensity experienced by the patients, as measured by a visual analogue scale (VAS). Patients with AK experienced more pain than those with BD or BCC. The mean VAS score was higher when treating lesions located on the head than when treating lesions on the trunk or the extremities. Also, treatment of large skin areas resulted in more pain than treatment of small areas, and men experienced more pain than women. The pain experienced by the patients seems not to correlate with treatment dose, skin type, age or fluorescence intensity. Several modalities of pain reduction during ALA-PDT have been tried. Reduction of pain during PDT has been managed by using 2% lidocaine gel, 10% lidocaine spray, EMLA (2.5% prolocaine/2.5% lidocaine) ointment, 1% lidocaine (i.c.) and 2% mepivacain (i.c.). and ALA gel combined with compressed air cooling. In practice the use of 2% xylocaine gel is applied immediately after the first unbearable pain sensation presents itself. This application has not been shown to interfere with the action of 5-ALA or its derivates. Other side effects have been described. The most frequent cosmetic problems are residual hyperpigmentation and hypopigmentation induced by PDT. These pigment changes are likely to resolve within a few months after irradiation. Patients with dark skin are most at risk.

Koebner reaction within PDT-treated areas, followed by severe reactivation of psoriasis, has also been reported. Development of malignant melanoma at the site of treatment with topical ALA-based PDT for AK and superficial SCCs has been described.

Diagnostic procedures

Besides its usefulness in oncological therapy, ALA also has a unique feature that can be exploited for diagnostic purposes (C. Abels, Germany). This procedure, termed photodiagnosis, helps to delineate poorly defined tumour borders before the use of invasive treatment modalities. By using a CCD camera system together with digital imaging, the contrast of the acquired fluorescence images can be significantly enhanced. This allows better identification of tumour outlines.

PDT in private practice

PDT is increasingly being employed in practice and is at present regarded as a safe and effective treatment option and a useful complement to the established therapeutic management of several skin diseases (J. Funck, Norway). The therapeutic considerations that need to be taken into account are the rate and magnitude of response, duration of remission, short-and long-term safety, costs, practicability and patients' satisfaction. The optimal application time and concentration are not known precisely and may differ depending on the characteristics of the target cells. The development of topical PDT has been enhanced by the advantages of being non-invasive, well tolerated in slow healing sites and tissue sparing by leaving the skin surrounding the tumour intact and functional. In addition, several separate lesions can be treated simultaneously and the treatment can be repeated with good cosmetic results.