Photodynamic therapy in dermatology

Currently, topical photodynamic therapy (PDT) has received approval for the treatment of dermato-oncologic conditions like actinic keratoses, Bowen’s disease, in-situ squamous cell carcinoma and basal cell carcinoma in many countries all over the world. For many non-neoplastic dermatological diseases like localized scleroderma, acne vulgaris and viral warts a therapeutical benefit of PDT is evident, too. Unlike the formerly used, only systemically-applicable haematoporphyrin derivatives, the recently developed topical photosensitizers 5-aminolevulinic acid (ALA) or its methyl ester (MAL) induce photosensitizing porphyrins. Moreover, the latter do not induce strong generalized cutaneous photosensitization. Due to the easy accessibility of skin to light activation, incoherent lamps or LED arrays are suitable for PDT. The production of reactive oxygen intermediates like singlet oxygen depends on the applied light dose as well as the concentration and localization of the photosensitizer in the diseased tissue. Either cytotoxic effects resulting in tumor destruction or immunomodulatory effects improving inflammatory skin conditions are induced. Treating superficial non-melanoma skin cancer, PDT has been shown to be highly efficient despite the low level of invasiveness. The excellent cosmetic results after treatment are beneficial, too.

Key words: photodynamic therapy, aminolevulinic acid, methyl aminolevulinate, skin cancer, inflammatory dermatoses

Hermann von Tappeiner, director of the Institute of Pharmacology at the University of Munich, already coined the term “photodynamic reaction” 100 years ago. According to the observations of one of his doctoral students, Oscar Raab, the reaction was characterised as an oxygen dependent tissue reaction following photosensitization and irradiation with light [1, 2]. Oscar Raab could show in his experiments that acridine orange was lethal for paramecia in the presence of sunlight [1]. The toxicity of acridin orange on protozoa was not only dependent on the dye concentration, but also on the intensity of the ambient light. Von Tappeiner successfully treated, in cooperation with the dermatologist Jesionek, patients with topical Eosin solution (1-5%) suffering from lupus vulgaris, secondary syphilis and superficial skin cancer [2]. In 1911 Hausmann reported photodynamic effects on mice injected with hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure. The German researchers, Auler and Banzer, observed in 1942 the specific uptake of hematoporphyrin showing extensive edema and erythema after light exposure.

Today, it is known that PDT requires precisely the simultaneous presence of a photosensitizer, light and oxygen inside the diseased tissue. The photosensitizer is accumulated in the target cells and absorbs light of a certain wavelength. The energy is transferred to oxygen and highly reactive oxygen species – mainly singlet oxygen – are generated. Treating with appropriate light doses, the reactive oxygen species directly lead to cell and tissue damage by inducing necrosis and apoptosis and indirectly stimulate inflammatory cell mediators. Following lower light doses treating inflammatory dermatoses, immunomodulatory effects are induced. In the past decades, PDT has gained worldwide popularity, first as an experimental therapy for a variety of human cancers. Mainly porphyrins, chlorine derivatives or phthalocyanines have been studied so far, for primary or adjuvant cancer therapy [5]. However, for dermatological purposes, only hematoporphyrin derivatives like porphyrin sodium (Photofrin®) or protoporphyrin IX (PpIX)-inducing precursors like 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) are of practical concern. As systemic photosensitizing drugs induce a prolonged photosensitivity [6], topical photosensitizers are preferred for use in dermatology. Meanwhile drugs like ALA or MAL have reached approval status for epithelial cancers or their precursors throughout the world and there is growing interest in the use of PDT not only for non-melanoma skin cancer but also for other skin tumors like lymphoma or for tumor surveillance in transplant patients as well as for non-oncological indications [7-10].
Photosensitizers

Eosin red or erythrosine were the first dyes Georges Dreyer in Copenhagen and Albert Jesionek in Munich used at the beginning of the last century as topical “photosensitizers” to treat conditions like syphilis, lupus vulgaris, pityriasis versicolor, psoriasis, molluscum contagiosum or skin cancer [2]. However, due to recurrence and severe side effects these experiments were abandoned. Since 1908 the tumor localizing effects of porphyrins have been studied. In the late 1970s, hematoporphyrin derivative (HPD) based PDT for the treatment of skin cancer came up again [2-4]. The main problem in the use of HPD is the prolonged skin photosensitization which lasts for several weeks [11]. Topical application is not possible since the rather big molecules (tetrapyrrolic rings) do not penetrate the skin. Therefore the introduction of porphyrin precursors like ALA or later MAL by Kennedy and co-workers in 1990 was a significant milestone in the development of PDT in dermatology, as the small molecules easily penetrate the epidermis due to their low molecular weight [2, 12]. In the USA the 5-ALA hydrochloride (Levulan® Kerastick), is approved for photodynamic treatment of actinic keratoses in combination with blue light [5]. The 5-ALA based photosensitizers are not photoactive by themselves, but show a preferential intracellular accumulation inside the altered cells constituting the diseased tissue and are metabolized in the haem biosynthesis to photosensitizing porphyrins rather selectively inside these cells [2, 13]. If no surface illumination is given, the porphyrins are metabolized to the photodynamically inactive haem within 24 to 48 hours. Meso-tetrahydroxyphenylchlorin (mTHPC) or benzoporphyrin derivative monooacid A ring (Verteporfin) are other photosensitizers that have been applied systemically for the treatment of BCC and Bowen’s disease [14, 15]. In contrast to HPD, these second generation photosensitizers show only limited cutaneous phototoxicity.

Light sources

Following formation of the photosensitizing porphyrins, they can be activated by light of the appropriate wavelength. The porphyrins or related photosensitizers with a tetrapyrrolic structure exhibit a very typical absorption spectrum with the highest peak at approximately 405 nm, the so called Soret-band. Besides, several Q-bands exist, the last having an absorption peak at 635 nm. Although the peak is much smaller than that at 405 nm, this wavelength is preferentially used for irradiation since light in the red spectrum shows the best tissue penetration [16, 17]. However, blue light (BLU-U, DUSA Pharmaceuticals, Florida, USA) is approved in the USA in the combination with 5-ALA hydrochloride (Levulan® Kerastick) for photodynamic treatment of non-hyperkeratotic actinic keratoses [5, 18]. In addition, white light sources or green light sources also exist for PDT. However, it has been demonstrated in a comparative trial that light at shorter wavelengths is less effective in the treatment of Bowen’s disease at a theoretically equivalent dose; therefore only the use of red light is recommended for PDT of skin tumors [19, 20]. With red light, non-melanoma skin cancer up to a thickness of 2-3 mm can be treated, thicker lesions require multiple treatments or tissue preparation (debunking) prior to PDT [21-23]. For irradiation in PDT, lasers and incoherent light sources have been used [24-27], Pulsed laser light sources matching one of the Q-bands at 585 nm have been evaluated with equal results compared to an incoherent light source in the treatment of AK [26]. Although not ideally matching the porphyrin absorption spectrum, the use of a long pulsed dye laser at 595 nm also seems to be effective for the same indication [28]. However, incoherent light-sources exhibit fundamentally different irradiation characteristics as compared to lasers. As coherence is lost within less than a millimetre of penetration into skin, this property is not mandatory for PDT [27]. Irradiation with incoherent light sources is more reliable, simpler, and cheaper and usually shows similar efficacies as compared to laser irradiation [29, 30]. Therefore, the gold standard in topical PDT are incoherent light sources, either lamps (e.g. PDT 1200L, Waldmann Medizintechnik, Germany) or LED’s (light emitting diodes) (e.g. Aktilite™, Galderma, France; Omnilux PDT™, Phototherapeutics, UK), which match the absorption maxima of the ALA- or MAL-induced porphyrins and accomplish the simultaneous irradiation of larger areas [17, 25, 30-32]. For tissue destruction, treating malignant tumors, a light dose – using broad spectrum red light (580-700 nm) – of 100-150 J cm–2 (100-200 mW cm–2) is chosen. For the more narrow emission spectra of the LED systems (bandwidth approx. 30 nm) the values are significantly lower (37-50 J cm–2). The light intensity should not exceed 200 mW cm–2 to avoid hyperthermic effects [17, 30]. For inflammatory dermatoses a light dose of 10-40 J cm–2 and a light intensity of 50-70 mW cm–2 are sufficient (broad spectrum red light, usually multiple treatments). During irradiation, both the patient and clinic staff should be wearing protective goggles in order to avoid the risk of eye damage [33].

Mechanism of action

In the presence of oxygen, the activation of a photosensitizer by light of the appropriate wavelength leads to the generation of reactive oxygen species (ROS), in particular singlet oxygen. Depending on the amount and localization in the target tissue these ROS modify either cellular functions or induce cell death by necrosis or apoptosis [5, 10, 13]. There is a need for heme and related molecules in fast proliferating, relatively iron-deficient tumor cells of epithelial origin. Therefore intracellular uptake of heme precursors like ALA or MAL is eased, thus resulting in a preferential sensitization of those cells. The same applies for the target cells constituting inflammatory dermatoses. Therefore, tissue damage is mostly restricted to the sensitized cells almost omitting the surrounding tissue, especially cells of mesenchymal origin like fibroblasts, resulting in an excellent cosmesis [20]. Aside from two case reports with possible coincidence, no further reports on the carcinogenic potential of ALA/MAL-PDT have been published [20]. Moreover, in a recent study even long-term topical application of ALA and subsequent irradiation with blue light in a hairless mouse model did not induce skin tumors [34]. Stender et al. even showed a delay in photo-induced carcinogenesis in mice following repetitive treatments with ALA-PDT [35].
Practical aspects of topical PDT

As it could be shown that hyperkeratosis is the reason for a poor response to PDT of AKs localized on the hands [13], keratolysis should be performed in hyperkeratotic lesions prior to incubation with the aid of a gentle abrasion or a non-bleeding curettage [23, 32, 33, 36]. Overnight incubation with an ointment for easy mechanical removal might also work. Extemporaneous ALA preparations are mostly applied to the lesions with little overlap to the surrounding tissue for 4-6 hours prior to irradiation under occlusion and in addition with a light protective dressing or clothing [13]. For the licensed MAL formulation (Metvix®, Galderma, France) a shorter incubation time of three hours is sufficient, due to preferential uptake and higher selectivity [37, 38]. The entire area here is also covered with an occlusive foil to allow for better penetration (table 1; figure 1).

The most important side effects of PDT are stinging pain and a burning sensation. Even if they are usually restricted to the time span of irradiation and a couple of hours thereafter [20], they often limit the patients’ compliance. Especially if an extended irradiation field is selected, administration of analgesics is often necessary [39]. Pain perception can also be alleviated by concurrent cold air analgesia which improves the tolerability of ALA/MAL-PDT [40]. Application of topical analgesics like eutectic mixtures of lidocaine/prilocaine prior to irradiation interacting with the incubation period of ALA/MAL are not recommended since their high pH might chemically inactivate the photosensitizer.

Following tumor treatment, localized erythema and edema in the treated area are usually seen, followed by a dry necrosis sharply restricted to the tumor bearing areas over the next days. After 10-21 days, the crusts formed come off and, usually, complete re-epithelialization is observed.

Table 1. Country-specific approval of topical MAL- (Metvix®) or ALA- (Levulan® Kerastick) PDT for the treatment of different oncologic and nononcologic diseases (Y = yes; N = no). (as of 9/05)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Approval MAL (Europe, NZL, AUS)</th>
<th>Approval ALA (USA, CDN)</th>
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<tr>
<td><strong>Oncologic Indications</strong></td>
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<tr>
<td>Bowen’s Disease</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Actinic Keratosis</td>
<td>Y (also USA)</td>
<td>Y (in combination with blue light)</td>
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<tr>
<td>Squamous Cell Carcinoma</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Basal Cell Carcinoma</td>
<td>Y</td>
<td>N</td>
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<tr>
<td><strong>Nononcologic Indications</strong></td>
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<td></td>
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<tr>
<td>Psoriasis vulgaris</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Vulgar warts</td>
<td>N</td>
<td>N</td>
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<td>Genital warts</td>
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<tr>
<td>Acne vulgaris</td>
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<td>Morphea</td>
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<td>Lichen sclerosus</td>
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<td>Actinic cheilitis</td>
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<td>Nevus sebaceus</td>
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<tr>
<td>Epidermodysplasia verruciformis</td>
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single treatment [20, 44]. For illumination purposes, both red (635 nm) or blue lights (417 nm) have been used [18, 44]. Green light may also be effective, but the user should always bear in mind that the use of non-red light is not suitable for indications other than AK, due to the lack of sufficient tissue penetration [13].

In a European, multicenter, randomized prospective study, MAL-PDT was compared to cryosurgery in the treatment of AK. A total of 193 patients (95%) with 699 lesions completed the trial. Patients received either a single treatment with MAL-PDT (repeated after one week in 8% of cases) or a double freeze-thaw course of liquid nitrogen cryosurgery. MAL was applied for 3 hours after slight lesion preparation, followed by illumination with broad spectrum red light (75 J cm$^{-2}$). A follow-up visit was performed 3 months post-treatment. The efficacy for MAL-PDT (single application) was 69% vs. 53% for cryosurgery, which was of no statistical significance. Thin lesions on the scalp had the highest response rates (80% and 82% for PDT and cryosurgery, respectively). Cosmetic outcome, as judged by the investigator, was superior for MAL-PDT (96%) vs. 81% for cryosurgery, respectively). Cosmetic outcome, as judged by the investigator, was superior for MAL-PDT (96%) vs. 81% for cryosurgery, respectively.

In chronology, a comparable trial was conducted in Australia. In this study MAL-PDT was used as a dual cycle, with two treatment sessions, one week apart. PDT was compared to a single course of cryosurgery or placebo in 204 patients. Lesion response was also assessed after 3 months. A significantly higher complete remission rate with MAL-PDT was observed (91%) vs. 68% with cryosurgery and 30% with placebo. The cosmetic result was rated excellent in 81% of MAL-PDT patients vs. 51% treated with cryosurgery [45].

A multicenter, randomized, double-blind, placebo-controlled study with two MAL-PDT cycles was performed in 80 patients with AK in the USA. PDT treatment parameters were similar to the above mentioned trials. Assessment after 3 months revealed a complete lesion response rate of 89% for MAL-PDT vs. 38% for placebo. An excellent or good cosmetic outcome was reported in more than 90% of MAL-treated patients [46].

Dragieva et al. focused in their recent prospective, randomized, double-blind, placebo-controlled study on MAL-PDT in the treatment of AK (n = 129) in 17 transplant recipients. As transplant recipients have an increased propensity to develop multiple AK, which demonstrate an increased transformation rate into invasive squamous cell carcinoma, an effective treatment is imperative. Sixteen weeks following illumination with red light (incoherent light source, 75 J cm$^{-2}$, 80 mW cm$^{-2}$) they observed complete remission in 13 out of 17 patients. They concluded that MAL-PDT is a safe and effective treatment for AK in transplant recipients that may reduce the risk of transformation of AK to squamous cell carcinoma [9].

Also, for ALA-PDT in the treatment of AK a randomized, placebo-controlled, uneven-parallel-group study was published recently. In 243 patients, clinical response, based on lesion clearing, was assessed at week 8 and 12. Patients were randomized to receive either vehicle or ALA (Levlan® Kerastick, DUSA, Wilmington, USA), followed within 14-18 h by illumination with visible blue light (BLU-1® DUSA, low pressure fluorescent lamps). Complete response rates for ALA-PDT patients with ≥ 75% of the treated lesions clearing at weeks 8 and 12 were 77% and 89%, respectively. In the placebo group, clearing rates were 18% and 13%. The 12 week clearing rates included 30% of patients who received a second ALA-PDT course. Moderate to severe discomfort during illumination was reported by at least 90% of patients; however, only 3% of patients required discontinuation of therapy [18].

For the purpose of lowering the amount of side effects of ALA-PDT, shorter incubation periods (1, 2, 3 h), in conjunction with pre-treatment with 40% urea in order to enhance ALA penetration and the use of topical 3% lidocaine hydrochloride to decrease discomfort were also evaluated. One and 5 months after therapy in 18 patients with at least 4 non-hypertrophic AK a reduction of lesions up to 90% in the target area was observed. No difference was seen between the three incubation periods nor did pre-treatment with urea or lidocaine have an influence on the therapeutical outcome [39].

**Bowen’s disease & Initial squamous cell carcinoma**

Topical PDT using 20% ALA has been extensively assessed in Bowen’s disease with more than 14 open and three randomized comparison studies [9, 19, 20, 47]. Cure rates reported so far are the best for all epithelial cancers or precursors (up to 100%). In a recent study by Salim et al., ALA-PDT was compared to topical 5-fluorouracil (5-FU). In this bi-center, randomized, phase III trial, 40 patients with one to three lesions of previously untreated, histologically proven Bowen’s disease received either PDT or 5-FU. ALA 20% in an o/w-emulsion was applied 4 h prior to illumination with an incoherent light source (Paterson lamp, Photo therapeutics, UK; $\lambda_{\text{cen}} = 630 \pm 15$ nm; 50-90 mW cm$^{-2}$, 100 J cm$^{-2}$). Treatment with 5-FU was once daily in week one and then twice daily during weeks 2-4. At first follow up at week 6, both ALA-PDT and 5-FU application were repeated, if required. Twenty-nine of 33 lesions (88%) treated with PDT showed complete response, vs. 67% after 5-FU (22 of 33). After one year of follow-up, further recurrences reduced the complete clinical clearance rates to 82% and 42%, respectively [48].

**Basal cell carcinoma**

Various studies concerning ALA/MAL-PDT for BCC have been performed in the past years [6, 13, 22, 23, 47, 49-51]. The weighted average complete clearance rates, after follow-up periods varying between 3 and 36 months, were 87% in 12 studies treating 826 superficial BCCs and 53% in 208 nodular BCCs [6, 20]. Available compiled data from other trials have shown an average of 87% for superficial BCCs, and 71% for nodular BCCs [5].

In order to ameliorate poor outcome after PDT of thicker BCC lesions, Thissen et al. [23] treated 23 patients with 24 nodular BCCs once with ALA-PDT (incoherent red light; 100 mW cm$^{-2}$, 120 J cm$^{-2}$) three weeks after debulking of the BCCs. The former tumor areas were excised three months later and histopathologically evaluated for residual tumor. Twenty-two (92%) of the 24 nodular BCCs showed both clinically and histologically a complete response. In a prospective phase III trial comparing ALA-PDT with cryosurgery, Wang et al. [51] included 88 superficial and nodular BCCs. Recruited individuals were only allowed to have one lesion included in the trial. A 20% ALA/water-in-oil cream was applied for 6 h under an occlusive dressing, followed by irradiation with a laser at 635 nm (80 mW cm$^{-2}$, 60 J cm$^{-2}$). In the cryosurgery arm, lesions were treated with liquid nitrogen in the open spray technique.
using two freeze-thaw cycles for 25-30 s each time. After 3 months, punch biopsies were performed and revealed a recurrence rate of 25% in the PDT group and 15% in the cryosurgery group. However, the clinical recurrence rates were only 5% for ALA-PDT and 13% for cryosurgery. The discrepancy between the clinical appearance of the treated lesion and the actual status in histology is problematic, as tumor recurrence can be masked. In the PDT treated group a better cosmetic outcome and a shorter healing time was documented.

Solèr and colleagues [22] studied the long term effects of MAL-PDT in 59 patients with 350 BCCs. Nodular tumors were curetted before PDT and MAL (160 mg/g) was applied to all to all tumors for 24 h or 3 h prior to irradiation with a broad-band halogen light source (50-200 J cm⁻²). Patients were followed for 2-4 years (mean 35 months). Overall cure rate was 79%, cosmetic outcome was excellent or good in 98% of the completely responding lesions.

In a recent open, uncontrolled, prospective, multicenter trial, patients with both superficial and/or nodular BCC who were at risk of complications, poor cosmetic outcome, recurrence and/or recurrence using conventional therapy were studied. Ninety-four patients were treated with a single cycle of MAL-PDT involving two treatment sessions one week apart, and followed up at three months, at which time non-responders were retreated. The clinical lesion remission rate after three months was 92% for superficial BCC, 87% for nodular BCC. The histological cure rate at this time point was 85% in superficial BCC and 75% in nodular BCC. At 24 months after treatment, the overall lesion recurrence rate was 18% [49]. In another European multicenter, open, randomized trial, MAL-PDT for nodular BCC was compared with surgery. A total of 101 patients were included and received either PDT twice, 7 days apart, or surgical excision. The primary end point of this trial was the clinically assessed lesion clearance at 3 months after treatment, besides cosmesis. The 3 month cure rate was similar with MAL-PDT or surgery (91% vs. 98%), the 24 month recurrence rate was 10% with MAL and 2% with surgery. The cosmetic result was rated good/excellent in 85% of the patients receiving PDT vs. 33% with surgery [50]. In a comparative trial in Australia, MAL-PDT for nodular BCC was compared to placebo. Lesions from 66 patients were treated either with two sessions of either placebo or MAL-PDT in a randomized, double-blind controlled study. If there was no complete response 3 months after initial treatment, lesions were excised. After six months, complete remission rate was 73% for MAL-PDT compared to 21% of placebo [38].

ALA-PDT can be used also for adjuvant therapy in combination with Mohs micrographic surgery, as reported recently by Kuijpers et al. [52]. In four patients, who underwent Mohs micrographic surgery for extensive BCC, first the central infiltrating tumor part was excised. After re-epithelialization, ALA-PDT of the surrounding tumor rims (2-5 cm) bearing remaining superficial tumor parts, was performed. This led to a complete remission of the tumors with excellent clinical and cosmetic results (follow-up period up to 27 months) [52]. However, even if all clinical studies qualify PDT as an effective treatment of BCC, Mohs micrographic surgery shows generally higher cure rates as compared to PDT. Besides, the relatively short follow up of most of the studies performed has to be considered. Mandatory indications for surgical treatment are different histological subtypes like pigmented or morpheic BCCs or BCCs located in the area of the facial embryonic fusion clefts as well as all BCCs thicker than 3 mm if no debulking procedure is performed prior to PDT.

**Therapeutic applications – non-oncologic indications**

In contrast to PDT of tumors, where cellular destruction is the main goal of the therapy, in PDT of inflammatory skin conditions the modulation of cellular functions is probably the main role. The therapeutic protocols differ significantly from those used for the treatment of tumors. Significantly lower doses of both light and photosensitizer are used in the context of a “low-dose-PDT” for the treatment of inflammatory skin conditions. However, multiple treatments are necessary to achieve the desired therapeutic effects with little or no side effects. So far, the best results for PDT in inflammatory skin conditions have been achieved with 5-aminolevulinic acid (ALA). However, for non-oncologic skin disease, there is a lack of controlled clinical trials so far, but there are numerous publications reporting a remarkable therapeutic benefit following PDT of e.g. acne vulgaris, localized scleroderma, psoriasis or genital warts, with no severe side effects [53-56]. Therefore, it is very likely that PDT will also be of great value for a choice of non-oncologic indications.

**Psoriasis vulgaris**

The data provided in the literature for the treatment of psoriasis vulgaris is very controversial. It has been shown that ALA is capable of penetrating the parakeratotic stratum corneum in the area of a psoriatic plaque and selectively accumulating in the diseased tissue [57, 58]. Boecknke et al. [59] compared the efficacy of ALA-PDT in three patients with a conventional topical treatment using dithranol in a half-side trial. The lesions were incubated with a 10% ALA-ointment for 5 hours followed by an irradiation with an incoherent light source (600-700 nm, 70 mW cm⁻², 25 J cm⁻²). This treatment was performed once weekly for three weeks, the plaques on the other side received anthraline on a daily base. The time to reach complete remission of psoriatic plaques was similar in both treatment settings. In a recent study performed by Collins and co-workers, 22 patients with psoriasis were treated with ALA-PDT [60]. After application of a 20% ALA-preparation for 4 hours the plaques were illuminated using an incoherent light projector (400-650 nm, 300 mW cm⁻², 2-16 J cm⁻²). In 7 of the 22 patients some of the treated plaques healed. In a further study the same working group studied the effect of multiple treatments with ALA-PDT [61]. Ten patients with chronic plaque-stage psoriasis have been treated up to 3 times a week for a maximum of 12 treatments. A 20% ALA-emulsion was applied for 4 hours, afterwards the plaques were irradiated with a broadband light source at 15 mW cm⁻² and 8 J cm⁻². In eight patients a clinical success was achieved. However, all patients complained of pain during the irradiation process. Beatti et al. [62] reported a lack of efficacy and tolerability of topical PDT for psoriasis in comparison with narrowband UVB.
phototherapy. Furthermore, Radakovic-Fijan et al. [63] performed a randomized, intra-patient comparison study on topical ALA-PDT in psoriatic patients and documented not only an unsatisfactory clinical response but also frequent occurrence of pain during and after irradiation. They concluded topical ALA-PDT to be an inadequate treatment option for psoriasis.

The pain seems to be dose-dependent for both the photosensitizer and the light and it fades within a period of two days after therapy. It is therefore important to study whether both light dose and drug concentration can be lowered following the concept of a “low-dose-PDT” with the goal of reduction of pain without hampering with the efficacy of the therapy.

Another side effect reported in the literature is Koebnerization [64]. One patient receiving PDT with ALA for the treatment of actinic keratosis and initial squamous cell carcinoma developed psoriatic lesions on her lower leg two days after PDT.

The impact of PDT on psoriatic lesions is yet not fully clear since the therapeutic protocols used differ significantly and so far no controlled clinical trials with high numbers of patients are available. However, potential advantages do exist for PDT in contrast to the UV-irradiation, as there is no evidence of an increased risk of cutaneous cancer developing after PDT. Some investigations also show that the number of treatments needed for therapeutic success seems to be lower, in comparison to PUVA-therapy.

**HPV-induced skin diseases**

Vulgar warts on hands and feet, plain warts or genital warts (condylomata acuminata) are common skin diseases induced by human papilloma viruses (HPV) [65]. Even after surgical removal or application of cytotoxic drugs a high rate of recurrences can be observed. Since the fast proliferating cells in viral acanthomas accumulate ALA-induced PpIX selectively [66, 67] and since ALA-PDT has virucidal properties [68] PDT is introduced as a possible alternative treatment modality.

**Vulgar warts**

Kennedy et al. did not achieve success in the treatment of vulgar warts with ALA-PDT in their study published 1990 [12]. Correspondingly, Amman et al. did not report successful topical ALA-PDT in the treatment of recalcitrant vulgar warts [69]. Only in one out of six patients was a complete remission achieved within two months after PDT [69]. The reason for the treatment failures was probably the less effective cutaneous penetration of ALA due to the prominent hyperkeratosis in vulgar warts. Smetana et al. tried to increase the effectiveness of ALA-PDT by adding the penetration enhancers EDTA (2%) and DMSO (2%). With this formulation they were able to treat successfully widespread vulgar warts in a patient who received a kidney transplant. Within a follow-up period of two years no recurrence was observed [68].

Stender et al. conducted a comparative trial in 30 patients with recalcitrant warts. After incubation with a 20% ALA-cream for five hours irradiation was performed using a slide protector with different wavelengths and a total light dose of 40 J cm–2. Previous to ALA-PDT, keratolysis of the warts was performed [70]. Following PDT with white light, which was performed three times, complete remission was significantly higher (CR 73%) than after PDT performed three times with blue light (CR 28%) or red light (CR 42%) or with the use of cryotherapy as a comparative treatment modality (CR 20%). Within the follow-up period of 12 months no further recurrences were observed. This study was then followed by a double-blinded, randomized trial by the same working group in 45 patients, which consolidated the results of the first pilot-trial [55]. Also in this trial it could be shown that ALA-PDT is successful in the treatment of recalcitrant warts of the hand and the soles of the feet. Irradiation was performed with an incoherent light source (Waldmann PDT 1200L, 590-700 nm) at a light intensity of 50 mW cm–2 and a total light source of 70 J cm–2. The procedure was repeated after one and after two weeks. If the warts were still present after 7 weeks, a therapeutic cycle (3 treatments in weekly increments) was again performed. The patients were advised to debride their warts prior to PDT. The trial resulted in a complete remission of warts in 56% of cases in the ALA-PDT treated group in comparison to 42% in the placebo group. A major side-effect of this treatment is pain [55].

Fabbrocini et al. [71] performed another placebo-controlled trial where 64 plantar warts were treated with 20% ALA after keratolysis. 57 warts served as controls (treated only with the emollient without drug). Irradiation was performed with an incoherent light source (400-700 nm, 50 J cm–2), it was repeated depending on the results up to 3 times per week within a period of 3 weeks. Two months after therapy 75% of the warts treated with ALA-PDT showed complete remission, whereas only 22.8% of the warts treated with placebo showed complete remission.

These results show that ALA-PDT in combination with a sufficient keratolysis is a successful alternative in the treatment of recalcitrant warts. Again, the main drawback is pain during irradiation which probably will hinder a broad use of PDT, especially in children.

**Genital warts**

Most of the destructive therapeutic modalities of anogenital condylomata like electrosiccation or vaporisation using a CO2-laser only lead to a destruction of the visible part of the warts, whereas subclinical lesions will not be treated effectively and cause the high rate of recurrence. ALA-PDT could be of great interest for this indication especially due to the selective destruction of subclinical virus-shedding areas, helping to reduce the high rate of recurrence.

Since a selective enrichment of PpIX in warts is the main prerequisite for the therapeutic efficacy, Fehr et al. [66] studied the fluorescence of PpIX after topical application of ALA in vulvar condylomata in 22 patients. Three to six hours after application of ALA a homogeneous distribution of PpIX was seen in the epidermis. After 24 hours fluorescence was only seen in the region of the granular layer. Similar results were reported by Ross et al. [67]. They were able to show a selective accumulation of PpIX in condyloma after topical application of ALA. Two hours following start of incubation, a higher selectivity compared to the surrounding normal skin was already achieved. In a pilot study, 7 patients with anogenital warts were treated with a cream containing 20% ALA in combination with lidocaine hydrochloride. The incubation time was 14 hours. After this time period a local anaesthetic was again applied for an additional two hours. Afterwards the area was irradiated with an argon ion-pumped dye laser (630 nm, 75-150 mW cm–2, 100 J cm–2). Four out of seven patients treated with ALA-PDT showed a complete remission [72]. The most important goal in the treatment of anogenital warts is the...
reduction of the high rate of recurrences after conventional treatment modalities. Perhaps the combination of classic ablative treatments with PDT, which contributes to a selective destruction of subclinical virus-shedding areas, might be of help.

Acne vulgaris

PDT in the treatment of acne is based on the fact that Propionibacterium acnes contains endogenous porphyrins, in particular coproporphyrin III [56]. Therefore, visible as well as blue light phototherapy is effective. Hongcharu et al. [73] treated 22 patients with acne vulgaris on the back in an open, prospective trial with ALA-PDT. Eleven patients received a single treatment, the other 11 patients were treated 4 times. ALA (20%) was applied occlusively for 3 hours, afterwards the area was irradiated with red light (550-700 nm, 150 J cm⁻²). The phototoxic reaction after ALA-PDT was restricted selectively to areas containing sebaceous glands. The function of the sebaceous glands was altered and also the numbers of bacteria in the follicles was reduced. Histopathology showed acute cytotoxic damage of the sebaceous glands. Clinically a significant improvement of the inflammatory acne lesions was observed after ALA-PDT which was sustained after multiple PDT-sessions for more than 20 weeks. Although ALA-PDT was very effective in the treatment of acne, severe side effects were observed: pain, erythema, edema, transient hyperpigmentation, sometimes even blistering, pruritus or burning sensation or mild pruritus as well as transient hyperpigmentation in the treated area were reported as side effects during the irradiation sessions. Even after two years no further progression and recurrence was observed. However, in some patients new morphea lesions developed at sides previously not treated with PDT. The effectivity of ALA-PDT was also reported for lichen sclerosus [77]. Twelve women with lichen sclerosus and severe pruri
tus were treated with a 20% ALA-formulation followed by irradiation with light from an argon ion-pumped dye laser (635 nm, 70 mW cm⁻², 80 J cm⁻²). If the pruritus did not resolve after the first treatment, the patients were retreated within 1-3 weeks after the first therapy. PDT was tolerated well, even 6-8 weeks after the last session pruritus had improved in 10 out of 12 patients.

Conclusion

PDT in dermatology is approved for the treatment of superficial basal cell carcinoma, actinic keratoses and also Bowen’s disease, in many countries all over the world. Numerous publications have demonstrated the effectiveness of PDT and also for the treatment of other cutaneous malignancies and non-oncologic indications [10]. However, controlled clinical trials are required to clarify whether PDT of non-oncologic indications can demonstrate superiority over existing, approved therapeutic modalities. The proven advantages of PDT include the simultaneous treatment of multiple tumors and incipient lesions, relatively short healing times, good patient tolerance and an excellent cosmesis. Very promising is the potential tumor control in immunocompromised patients (i.e. transplant recipients). Cost-effectiveness analysis indicates that with relatively low costs for permanent equipment, topical PDT is probably no more expensive than conventional therapy when its lower side-effect profile is considered [20].

References

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