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REVIEW ARTICLE

Photodynamic Therapy for Non-melanoma Skin Cancer

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Photodynamic therapy is a treatment modality that has been shown to be effective mainly for the dermato-oncologic conditions: actinic keratosis, Bowen's disease, *in situ* squamous cell carcinoma and basal cell carcinoma. Recent work has focused on the development and evaluation of topical photosensitizers like the haem precursor 5-aminolevulinic acid or its methyl ester, both inducing photosensitizing porphyrins. These drugs do not induce strong generalized cutaneous photosensitization, unlike the systemically applied porphyrins or their derivatives. For dermatological purposes incoherent lamps or light-emitting diode arrays can be used for light activation. Cure rates reported for very superficial lesions (tumour thickness <2–3 mm) are comparable to those achieved by other therapeutic modalities. Photodynamic therapy is a minimally invasive therapy associated with excellent cosmetic results. For actinic keratosis and basal cell carcinoma, methyl aminolevulinate-photodynamic therapy is already approved in Europe, Australia and New Zealand, and is now also approved for actinic keratosis in the US. ***Key words: photodynamic therapy; fluorescence detection; aminolevulinic acid; methyl aminolevulinate; skin cancer.***

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At the beginning of the 20th century Hermann von Tappeiner, then director of the Institute of Pharmacology of the University of Munich, first coined the term 'photodynamic reaction' (1). Already at that time it was known that photodynamic therapy (PDT) required the simultaneous presence of a photosensitizer, light and oxygen inside the diseased tissue. In recent years, PDT has gained worldwide popularity, first as an experimental therapy, then as a primary or palliative therapy for many human cancers. Mainly porphyrins, chlorin derivatives or phthalocyanines have been studied so far for primary or adjuvant cancer therapy (2). However, for dermatological purposes, only haematoporphyrin derivatives like porfimer sodium (Photofrin®) or protoporphyrin IX (PPIX)-inducing precursors like 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) are of practical concern. The main drawback for systemic photosensitizing drugs is their prolonged generalized phototoxicity (3). Therefore topical photosensitizers are preferred for use in dermatology. Meanwhile drugs like MAL have reached approval status for epithelial cancers or their precursors throughout the world, ALA in the US, and there is growing interest in the use of PDT not only for non-melanoma skin cancer but also for other skin tumours like lymphoma or for tumour surveillance in transplant patients (4–6).

PHOTOSENSITIZERS

The first drugs used for PDT were topically applied dyes like eosin red or erythrosine. Those photosensitizers were used exactly 100 years ago by Georges Dreyer in Copenhagen and Albert Jesionek in Munich (1903/1904) to treat conditions like pityriasis versicolor, psoriasis, molluscum contagiosum, syphilis, lupus vulgaris or skin cancer (1). Unfortunately the experiments were abandoned due to lack of long-term remissions and severe side effects. Since 1968 the tumour localizing effects of porphyrins were studied. This resulted in a renaissance of PDT in the late 1970s by Thomas Dougherty who used haematoporphyrin derivative (HPD) and later its purified derivative porfimer sodium for the treatment of primary cancer of the skin or cutaneous metastases (1, 2). The main problem in the use of HPD or porfimer sodium is the prolonged skin photosensitization, which lasts for several weeks (7). A desired topical application is also not possible since the rather big molecules (tetrapyrrol rings) do not penetrate the skin. Therefore the introduction of porphyrin precursors like ALA by Kennedy and co-workers in 1990, and later MAL, both small molecules of low molecular weight which easily penetrate abnormal epidermis overlying skin tumours, were significant milestones in the development of PDT in dermatology (1).

The most interesting aspect of those porphyrin precursors is their tumour selectivity. After topical application, both ALA and MAL are mainly taken up by cells of epithelial origin and are converted into photosensitizing porphyrins (8). MAL has shown a higher selectivity for tumour cells compared with ALA,

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explained by a different mechanism of cellular uptake as a result of an increased lipophilic structure. Unaffected adjacent epidermis and mesenchymal cells, like fibroblasts, show a much less pronounced porphyrin production, thus leading to a high ratio between tumour and surrounding tissue (9). This phenomenon enables then both selective detection of lesions (fluorescence detection) and selective destruction with minimal harm to the surrounding tissue when the consecutive illumination is performed.

Currently in Europe the only photosensitizer approved in dermatology is methyl aminolevulinate (MAL, Metvix®, Photocure AS, Oslo, Norway, and Galderma SA, Paris, France). Metvix® is approved for PDT of superficial and nodular basal cell carcinoma (BCC) and actinic keratoses (AK) in combination with red light. In the USA Metvixia®, in combination with red light, and Levulan® Kerastick™ (DUSA, Wilmington, MA, USA), containing 5-ALA hydrochloride, in combination with blue light, are approved for PDT of AK (2). The 5-ALA-based photosensitizers are not photoactive themselves, but show a preferential intracellular accumulation in the tumour cells and are metabolized by the haem biosynthesis into photosensitizing porphyrins (8–11). If no surface illumination is given, PPIX is metabolized to the photodynamically inactive haem within the next 24–48 h (3).

Meso-tetrahydroxyphenylchlorin (mTHPC) or the benzoporphyrin derivative monoacid A ring (verteporfin) are other photosensitizers that have been applied systemically for the treatment of BCC and Bowen's disease (12, 13). In contrast to HPD, those second generation photosensitizers show only limited cutaneous phototoxicity.

LIGHT SOURCES

After the preferential synthesis of porphyrins inside the diseased tissue, the resulting photosensitizers can be activated by light. The porphyrins or related photosensitizers exhibit a very typical absorption spectrum with a high peak at approximately 405 nm, the so-called Soret-band. Visible blue light matching this band therefore can be used in combination with ALA for AK (14). Several so called Q-bands also exist, the last having an absorption peak at 635 nm. Although the peak is much smaller than that at 405 nm, this wavelength is predominantly used for illumination as light in the red spectrum shows the best tissue penetration (15, 16). It has been shown 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 tumours (10, 17). 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 (debulking) prior to PDT (18–20).

There is no difference regarding the profile of light necessary for a successful ALA- or MAL-PDT, and both laser and incoherent light sources can be used. Even 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 (21). Also the use of a long-pulsed dye laser at 595 nm seems to be effective for the same indication (22). However, the costs for purchasing and maintenance of these laser systems are substantially high.

The gold standards in topical PDT are light sources with wide illumination fields which accomplish the simultaneous illumination of larger areas, which is often needed in AK or Bowen's disease. Here incoherent light sources are preferred, either lamps (e.g. PDT 1200L, Waldmann Medizintechnik, Villingen-Schwenningen, Germany) or LEDs (light emitting diodes) (e.g. Aktilite™, Galderma or Omnilux™, Waldmann), which match the absorption maxima of the ALA- or MAL-induced porphyrins (5, 16, 23–25). For tissue destruction 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 approximately 30–40 nm) the values given are significantly lower (37–50 J/cm^2). However, therapeutic efficacy of broad-spectrum and narrow-spectrum lamps has not been compared yet. In any case, the light intensity should not exceed 200 mW/cm^2 so as to avoid hyperthermic effects (16, 23). During illumination, both the patient and clinic staff should be wearing protective goggles to avoid the risk of eye damage (26).

MECHANISM OF ACTION

Following activation of a photosensitizer with light of the appropriate wavelength, reactive oxygen species (ROS), in particular singlet oxygen, are generated. Depending on the amount and localization in the target tissue these ROS modify either cellular functions or induce cell death by necrosis or apoptosis (2, 6, 10). Interestingly, so far, apart from two case reports with possible coincidence, no further reports on the carcinogenic potential of ALA/MAL-PDT have been published (11). Moreover, in a recent study even long-term topical application of ALA and subsequent illumination with blue light in a hairless mouse model did not induce skin tumours (27). As proliferating, relatively iron-deficient tumour cells of epithelial origin are preferentially sensitized by ALA or MAL, tissue damage is mostly restricted to the tumour. This leads to a low risk of damage to the surrounding tissue resulting in an excellent cosmesis (11). In contrast to systemic photosensitizers, where vascular breakdown of the tumour

microcirculation is one of the main mechanisms of action of PDT, topical PDT has minimal effect on tumour vasculature (10).

FLUORESCENCE DETECTION

The aforementioned tissue selectivity of porphyrin induction can also be exploited for diagnostic purposes: after topical or systemic application, porphyrin-containing tissue can be illuminated with blue light at the Soret-band, thus leading to the emission of pink fluorescent light. The high tumour to surrounding tissue ratio then enables the delineation of the tumour (9, 28).

This procedure, called fluorescence detection (FD), can enable the dermatologist to perform either a guided biopsy or a controlled and complete resection of tumour, sparing unaffected tissue. By using a commercial digital CCD camera system, together with digital imaging, the contrast of the acquired fluorescence images can be enhanced significantly and allows the determination of a threshold, which can be utilized either for a directed biopsy or for preoperative planning when Moh's surgery is scheduled (29). Moreover, FD is probably a helpful tool to prove the efficacy of PDT. At present, the routine employment of such systems is being assessed in prospective trials.

TOPICAL PDT – PRACTICAL ASPECTS

Prior to incubation with the photosensitizer in hyperkeratotic lesions, keratolysis or gentle abrasion should be performed with an ointment or wet cloth or by slight, non-bleeding curettage (19, 20, 26, 30). Hyperkeratosis is the reason for a poor response in AK localized on the hands (10). To date, ALA as hydrochloride has been applied in custom-made formulations, either creams or gels, sometimes with penetration enhancers, e.g. DMSO in a concentration of up to 20%. In the USA ALA is commercialized as Levulan® Kerastick™ with an incubation time of 14–18 h. The most widely available commercial product since June 2001 has been MAL, available as Metvix®.

ALA preparations are usually applied to the lesions with little overlap to the surrounding tissue for 4–6 h prior to illumination under occlusion and with a light protective dressing or clothing (10). For the MAL ointment the procedure is standardized and a shorter incubation time of 3 h is sufficient due to preferential uptake and higher selectivity (31, 32). The entire area is then covered with a foil to allow for better penetration.

Stinging pain and/or a burning sensation can be experienced during PDT, but are usually restricted to the period of illumination and a couple of hours thereafter (11). A recent publication has shown that MAL-PDT induces less pain than ALA (33). In some cases of PDT with extensive treatment fields, administration of analgesics is useful (34). Pain perception can also be reduced by concurrent cold air analgesia which has been shown to improve the tolerability of ALA/MAL-PDT (35). The application of local anaesthetics like eutectic mixtures of lidocaine/prilocaine prior to irradiation is generally not recommended. There is the possibility of interaction during the incubation period of ALA/MAL as the high pH of the anaesthetic might chemically inactivate the photosensitizing drug. After light exposure, localized erythema and oedema in the treated area are usually seen, followed by a dry necrosis sharply restricted to the tumour-bearing areas over the next few days. After 10–21 days, formed crusts come off and complete re-epithelialization is observed. During this phase, most patients report only slight discomfort.

Due to the selective photosensitization, restricted predominantly to cells of epithelial origin with sparing of fibroblasts or dermal fibres, usually no scarring or ulceration is observed clinically (10, 11, 19). Pigmentary changes are also rare and only of temporary duration. Irreversible alopecia has not yet been observed in the vast majority of the treated patients; however, due to the concomitant sensitization of pilosebaceous units, this potential risk should be considered (10, 11, 36).

Apart from patients with a known history of porphyrias or allergic reactions to the active ingredients of the applied sensitizers, no severe limitations to performance of ALA/MAL-PDT are known (37). The PDT procedure is repeatable and applicable even in areas with prior exposure to ionizing irradiation (38).

THERAPEUTIC APPLICATIONS

Approved indications for MAL in most European countries, New Zealand and Australia are AK and nodular or superficial BCC. Recently, MAL also received an approval in the US for AK where it will be marketed under the name Metvixia®. In addition, treatment of Bowen's disease is also indicated for PDT with ALA/MAL-induced porphyrins as recommended by evidence-based guidelines (11). However, for treatment of single lesions a variety of efficient alternatives exist, e.g. cryotherapy, surgery or drugs like 5-fluorouracil (5-FU), imiquimod or diclofenac-sodium. In contrast, for multiple lesions PDT has the potential of being a first-line therapy, in particular for AK of the scalp and face or in cases of basal cell naevus syndrome (2). In the following three sections, recent clinical trials published in peer-reviewed journals on the use of ALA/MAL-PDT for a variety of epithelial cancers will be presented. In respect of limited data on recurrence rates in the long-term follow-up, especially for BCC, published abstracts on follow-up data of those trials were also considered.

Basal cell carcinoma

ALA/MAL-PDT for BCC has been studied extensively in recent years in a variety of surveys (3, 10, 19, 20, 39–46). The weighted average complete clearance rates, after follow-up periods varying between 3 and 36 months, were 87% in 12 studies treating 826 superficial BCC and 53% in 208 nodular BCC (3, 11). Available compiled data from other trials have shown an average of 87% for superficial BCC, and 71% for nodular BCC (2) (see Table I).

In order to ameliorate poor outcome after PDT of thicker BCC lesions, Thissen et al. (20) treated 23 patients with 24 nodular BCC once with ALA-PDT (incoherent red light; 100 mW/cm^2, 120 J/cm^2) 3 weeks after prior debulking of the BCCs. Three months later the former tumour sites were excised and histopathologically evaluated for residual tumour. Twenty-two (92%) of the 24 nodular BCC showed a complete response, both clinically and histologically.

In a prospective phase III trial comparing ALA-PDT with cryosurgery, Wang et al. (42) included 88 superficial and nodular BCC. Recruited individuals were only allowed to have one lesion to be included in the trial. A 20% ALA/water-in-oil cream was applied for 6 h under an occlusive dressing, followed by illumination with a laser at 635 nm (80 mW/cm^2, 60 J/cm^2). In the cryosurgery arm, lesions were treated with liquid nitrogen by the open spray technique, using two freeze-thaw cycles of 25–30 s each. After 3 months, the clinical recurrence rates were only 5% for ALA-PDT and 13% for cryosurgery. However, on analysing punch biopsies a recurrence rates of 25% in the PDT group and 15% in the cryosurgery group were determined, but the results were not statistically significant ($p > 0.05$, Fisher's exact test). Besides better cosmetic outcome, healing time was also shorter in the PDT-treated group.

Solèr and colleagues (19) studied the long-term effects of MAL-PDT in 59 patients with 350 BCC. Nodular tumours were debulked before PDT and MAL (160 mg/g) was applied to all tumours for 24 h or 3 h prior to irradiation with a broadband halogen light source (50–200 J/cm^2). Patients were followed for 2–4 years (mean 35 months). Overall cure rate was 79% with a recurrence rate of 11% at 35 months and cosmetic outcome was excellent or good in 98% of the completely responding lesions (19).

In an open, uncontrolled, prospective, multicentre trial both patients with superficial and/or nodular BCC who were at risk of complications, poor cosmetic outcome, disfigurement and/or recurrence using conventional therapy were studied. Ninety-four patients were treated with a single cycle of MAL-PDT involving two treatment sessions 1 week apart, and followed up at 3 months, at which time non-responders were retreated. The clinical lesion remission rate after 3 months was 92% for superficial BCC and 87% for nodular BCC. Histological cure rate at this time point was 85% in superficial BCC and 75% in nodular BCC (95% confidence interval, 70–85%). At 36 months after treatment, the overall lesion recurrence rate was 23% in this difficult to treat population (39).

In a prospective, open-label, comparative, multicentre phase III study Basset-Seguin and colleagues treated a total of 118 patients with histologically confirmed superficial BCC. They were randomized to either cryotherapy ($n=58$) or MAL-PDT ($n=60$; 3 h application time, red light (570–670 nm) total light dose 75 J/cm^2). Lesion response and cosmetic outcome of lesions clinically in complete response were monitored continuously. Data from 107 patients have been analysed so far after 36 months, the recurrence rates were 22% for MAL-PDT and 19% for cryotherapy, which was not a statistically significant difference (43). It is important to

Table I. *Summary of results of clinical studies using topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate photodynamic therapy (MAL-PDT) for the treatment of basal cell carcinoma (BCC)*

Study	Indication/procedure	Sensitizer	Number of lesions	Lesion recurrence rates	Follow-up
Thissen 2000 (20)	Nodular BCC (debulking 3 weeks prior to PDT)	ALA	24	…	3 months (histological control)
Wang 2001 (42)	Superficial and nodular BCC	ALA	44	13%	12 months
Solèr 2001 (19)	Superficial and nodular BCC (debulking of nodular tumours prior to PDT)	MAL	350	11%	24–48 months (mean of 35 months)
Horn 2003 (39)	'Difficult-to-treat' superficial and nodular BCC	MAL	49	23%	36 months
Vincuillo 2005 (45)	'Difficult-to-treat' superficial and nodular BCC	MAL	148	24%	24 months
Rhodes 2004 (41)	Nodular BCC	MAL	53	10% ($p > 0.05$)	36 months
Basset-Seguin 2004 (43)	Superficial BCC	MAL	55	22% ($p > 0.05$) (with 1 MAL-PDT treatment session)	36 months

note that two MAL-PDT treatment sessions are indicated in the EU labelling for BCC and in this study patients were treated with one MAL-PDT session, repeated for patients with non-complete response at 3 months.

In another European multicentre, open, randomized trial, MAL-PDT for nodular BCC was compared with surgery. A total of 101 patients was included and they received either two courses of PDT, 7 days apart (75 J/cm^2 red light) or surgical excision. The primary end point of this trial was lesion clearance (assessed clinically) 3 months after treatment. The 3-month cure rate was similar with MAL-PDT or surgery (91% vs 98%), the 24-month lesion recurrence rate was 10% with MAL and 2% with surgery (estimated difference 95% CI, −1 to 22). The cosmetic result was rated good/excellent in 85% of the patients receiving PDT vs 33% with surgery (41).

In a comparative trial in Australia, MAL-PDT for nodular BCC was compared to placebo. Lesions from 66 patients were treated with two sessions of either placebo or MAL-PDT in a randomized, double-blind controlled study. In cases where there was no complete response 3 months after initial treatment, lesions were excised. After 6 months, histologically confirmed complete remission rate was 73% for MAL-PDT compared to 21% for placebo (31).

In the USA, a multicentre, randomized, double-blind, placebo-controlled trial comparing MAL-PDT and placebo-PDT in 65 patients with nodular BCC was performed. Forty-one BCC in 33 subjects received 2 cycles of MAL-PDT; 39 BCCs in 32 subjects received 2 cycles of placebo-cream PDT. Prior to PDT, surface debridement was performed. After 3 months, lesions with no clinical response were excised and lesions with partial response were retreated. Six months after the last treatment, BCC manifesting complete clinical response were excised to determine complete histological response. The overall complete histological response was 79% for MAL-PDT, compared with 33% for placebo-PDT, which was significantly superior ($p<0.001$) (31, 44).

In a prospective, multicentre, non-comparative study in Australia, MAL-PDT was used for BCC defined as 'difficult-to-treat', i.e. large lesions, in the H-zone, or in patients at high risk of surgical complications. Ninety-five patients with 148 lesions were included in the per protocol analysis. The histologically confirmed lesion complete response rate at 3 months was 89% (131 of 148). At 24 months, a cumulative treatment failure rate of 24% (36 of 148) was observed. Overall cosmetic outcome was judged as excellent or good in 84% of patients at 24 months. Interestingly, lesions located on the face/scalp region showed a significantly lower lesion complete response rate than that of lesions on the trunk/neck (at 24 months, 54% vs 88%, $p=0.009$) (45).

ALA-PDT can also be used for adjuvant therapy in combination with Mohs' surgery, as reported recently by Kuijpers et al. (46). In four patients, who underwent Mohs' micrographic surgery for extensive BCC, first the central infiltrating tumour part was excised. After re-epithelialization, ALA-PDT of the surrounding tumour rims (2–5 cm) bearing remaining superficial tumour parts was performed. This led to a complete remission of the tumours with excellent clinical and cosmetic results (follow-up period=27 months) (46).

Actinic keratoses

The efficacy of ALA-PDT has been observed in 6 open studies of 323 AK situated on the face and scalp in Caucasian populations. Clearance rates ranged from 71 to 100% after just a single treatment (11, 47). For illumination purposes, both red (635 nm) or blue light (417 nm) have been used (14, 47). Green light may also be effective, but the user should always bear in mind that non-red light should not be used for indications other than AK due to the lack of tissue penetration (10).

In a European, multicentre, 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 1 week in 8% of cases) or a double freeze-thaw course of liquid nitrogen cryosurgery. MAL was applied for 3 h 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% (95% CI, 64–74%) vs 75% (95% CI, 70–80%) for cryosurgery, which was not statistically significant. 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%, $p=0.035$) (32).

A comparable trial was conducted in Australia. In this study MAL-PDT was used as a dual cycle, with two treatment sessions, 1 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). Lesion response was statistically significantly higher for MAL-PDT compared with both placebo PDT ($p<0.001$) and cryotherapy ($p<0.001$). The cosmetic result was rated excellent in 81% of MAL-PDT patients vs 51% treated with cryosurgery as assessed by the investigator ($p<0.001$) or 76% vs 56% as assessed by the patient ($p=0.013$) (48).

Finally, a multicentre, 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 and a patient complete response rate of 82% for MAL-PDT (95% CI, 67–93%) vs 21% (95% CI, 21–37%) for placebo ($p=0.001$). An excellent or good cosmetic outcome was reported in 97% of MAL-treated patients (49).

Also for ALA-PDT a randomized, placebo-controlled, uneven-parallel-group study was published recently. In 243 patients clinical response, based on lesion clearing, was assessed by weeks 8 and 12. Patients were randomized to receive either vehicle or ALA (Levulan® Kerastick™), followed within 14–18 h by illumination with visible blue light. Complete response rates for ALA-PDT patients with $\geqslant$75% of the treated lesions clearing at weeks 8 and 12 were 77% and 89%, respectively. In the placebo group, clearing rates were 18% and 13% ($p<0.001$ at weeks 8 and 12). 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 (14).

For the purpose of lowering the amount of side effects of ALA-PDT, shorter incubation periods (1–3 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, an up to 90% reduction of lesions in the target area was observed. No difference was seen between the three incubation periods, nor did pre-treatment with urea or lidocaine have a positive influence on the therapeutic outcome ($p=0.99$) or the development of pain during irradiation ($p=0.65$) (34).

Bowen's disease and initial squamous cell carcinoma

Topical PDT using 20% ALA has been assessed extensively in Bowen's disease with more than 14 open and 3 randomized comparison studies (11, 17, 40, 50). 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. (50), ALA-PDT was compared to topical 5-FU. In this two-centre, randomized, phase III trial 40 patients with 1 to 3 lesions of previously untreated, histologically proven Bowen's disease received either PDT or 5-FU. ALA 20% in an oil/water emulsion was applied 4 h prior to illumination with an incoherent light source (Paterson lamp, Phototherapeutics, UK; $\lambda_{em}=630\pm15$ nm; 50–90 mW/cm^2, 100 J/cm^2). Treatment with 5-FU was once daily in week 1 and then twice daily during weeks 2–4. At first follow-up at week 6, both ALA-PDT and 5-FU applications 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 1 year of follow-up, further recurrences reduced the complete clinical clearance rates to 82% and 42%, respectively (50).

MAL-PDT has recently been studied in the largest existing study in the treatment of Bowen's disease. In this European multicentre (40 centres) comparative randomized controlled study performed in a total of 225 patients with 275 lesions, MAL-PDT induced a complete response in 93% of lesions compared to 86% with cryotherapy and 83% with 5-FU. At 12 months the overall lesion cure rates were 74% with MAL-PDT compared to 65% and 62% with cryotherapy and 5-FU (51).

CONCLUSION

The developments in PDT are continuously advancing. At present, ample data exist which demonstrate the usefulness of PDT for the treatment of cutaneous malignancies and benign conditions (6). So far the proven advantages of PDT include comparable clinical outcome to standard treatments, the simultaneous treatment of multiple tumours and incipient lesions, relatively short healing times, tumour control in immunocompromised patients (e.g. transplant recipients), high patient tolerance and an excellent cosmesis. Cost-effectiveness analysis indicates that with relatively low costs for permanent equipment, topical ALA/MAL-PDT is probably no more expensive than conventional therapy when its lower side effect profile is considered (11).

ALA/MAL-PDT has been rated to compete with concurrent standard medical therapies for indications like AK, BCC and Bowen's disease. However, as PDT is a treatment which, unlike surgery, does not provide histological control, lesions to be treated should be selected very carefully to exclude unresponsiveness (as in morpheic BCC) or inappropriate results (tumour thickness exceeding 3 mm). Especially for BCC, a final judgement on efficacy is still pending since the 5-year follow-up data on recurrence rates are not yet available. However, recently reported 36-month data show encouraging results with recurrence rates equivalent to that of currently standard therapies.

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