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Clinical Photodynamics

In Dermatology

An International Newsletter for PDT and FD in Clinical Practice

Editorial

This issue of ***Clinical Photodynamics*** features an extensive discussion of the 2010 Euro-PDT Congress, which was held in the stunning location of the Monte Carlo Bay Hotel, Monaco. In addition to the Congress report by Prof Sigrid Karrer, we have short reports of some of the prize-winning presentations and abstracts by their authors. Dr Colin Morton also provides a summary of the use of PDT in acral AKs, a difficult-to-treat condition that is attracting much interest from PDT clinicians keen to improve the treatment technique. If you attended the Euro-PDT this year and would like to add your own thoughts and comments to these reports, please do contact us, by e-mail, at: **eurocommunica@sky.com**.

The other two forthcoming PDT events of this year are the 19th EADV Congress in Gothenburg, Sweden, and the 8th Brixen/Bressanone Symposium on PDT and PD in Clinical Practice. It is, however, a great pity that these two key events of the PDT calendar are taking place at the same time - 6th-10th October for EADV, and 6th-9th October for Brixen. Therefore, for the benefit of our readers who don't possess a *Harry Potter*-style 'Time-Turner' and will thus be unable to be in the two places at once, we hope to be able to bring you reports on both these meetings in the next issue of ***Clinical Photodynamics***. Again, we invite you to send us your photos/comments on these two meetings.

Finally, we would like to repeat our ongoing invitation to readers to send us short reports on your own work, summaries of meetings that you have attended, comments on recently published PDT papers of particular merit, details of forthcoming events or even requests for help/co-operation between units. As the newsletter of I-PDT, we want to encourage a greater dialogue between PDT specialists around the world: this is **your** newsletter!

Rod Robinson, Publisher, Eurocommunica Ltd

10th Annual Congress of The European Society for Photodynamic Therapy

12–13 March, 2010 Monte Carlo Monaco

by: **Prof Dr Sigrid Karrer**
Regensburg, Germany

The 10th Annual Congress of Euro-PDT was held at the Congress Centre (see photo, middle right) of the truly splendid Monte Carlo Bay Hotel. The Congress President was **Prof JP Ortonne** (Nice, France). A one-day training course was organised in Nice before the Congress began, for those who wanted to learn the technique.

The Congress Centre, seen from the Hotel.

In this Issue

FRIDAY, 12th MARCH

After a welcome address by the President of the Euro PDT, **Prof Lasse R Braathen** (Tromsö, Norway and Bern, Switzerland), the first plenary session started with the topic: What is new in PDT technology? **Dr Sally Ibbotson** (Dundee, United Kingdom) gave the first talk on photosensitisers and focused on some more recent developments. As the currently used photosensitisers have several limitations (e.g. limited tissue penetration, drug instability, inefficient delivery systems or length of application time), the aim is to optimise both photosensitisers and their delivery. Currently, aminolevulinic acid (ALA) is licensed as Levulan® Kerastick™ in the USA, while methyl aminolevulate (MAL; Metvix®) is licensed in Europe, Australia and in the USA (in the latter only for actinic keratoses [AK]). In comparison to ALA, which is hydrophilic and unstable, MAL has the advantage of being more lipophilic. New formulations have been developed recently to improve ALA delivery. PDT with a self-adhesive ALA patch has been shown to be superior to cryotherapy and placebo, and has also shown better cosmetic results, compared to cryotherapy. In as yet unpublished studies, PDT with a newly developed ALA nanoemulsion has also shown good results in patients with AK. A bio-adhesive ALA patch (19mg/cm^2 per patch) was used to treat vulvar lichen sclerosus with good success. Sally Ibbotson then examined the use of transdermal photosensitiser delivery by ALA or MAL microneedles and current developments on a biodegradable polymeric microneedle. Iron chelators (e.g. CP94), which block the conversion of PpIX to haem, have been used to help optimise photosensitiser delivery. For antibacterial PDT, new photosensitisers are being developed, such as cationic photosensitisers (topical phenothiazines). Additionally, topical phthalocyanines, mTHPC liposomal gels, liposomal methylene blue hydrogels and platinum IV complexes were discussed. Thus, this talk gave an excellent overview on what is currently going on in the development and optimisation of photosensitisers.

Prof Lasse R Braathen then tried to answer the question: 'Short incubation – does it really work?' In a study with 110 patients with a total of 380 AKs, Metvix® at either 160mg/g or 80mg/g was applied for either 1 or 3 hours. Irradiation was then performed at 75J/cm^2, using the Curelight®. There were no statistically significant differences between these groups and complete response rates ranged between 74% (1 hour, 80mg/g) and 85% (3 hours, 160mg/g). As the 1-hour incubation showed similar good results to that of 3 hours, this shorter time might be sufficient when treating thin or moderately thin AK on warm days and could make practice organisation easier.

The Monte Carlo Bay Hotel, seen from the Congress Centre.

In the next talk, **Dr Merete Haedersdal** (Copenhagen, Denmark) asked the question: 'Light sources for PDT – do we always need a photosensitiser?' As PpIX is also produced naturally in the skin, mainly by micro-organisms (including *P. acnes*), these endogenous porphyrins could be directly targeted with light. Thus, the use of blue light without photosensitiser could show a temporary short-term efficacy in patients with acne vulgaris. However, when comparing an IPL alone with IPL plus photosensitiser, the combination therapy was more effective in clearing inflammatory acne lesions. A new concept to improve photosensitiser bioavailability into deeper skin layers was also presented. By using CO_2 fractional tissue ablation, vertical channels with deep holes can be built into the skin. This can enhance MAL-biodistribution and increase the uptake of the photosensitiser. In summary, Dr Haedersdal observed that only some skin conditions may be treated with PDT without a photosensitiser, whereas others require enhanced delivery of topically applied photosensitisers into deep skin layers.

In an effort to further simplify PDT and improve tolerability, **Dr Hans-Christian Wulf** (Copenhagen, Denmark) presented his studies on daylight-irradiation PDT. In this technique, only pre-treatment of AK and application of the cream is done in the clinic. Thereafter, the patients are asked to go home and stay outdoors. Complete response rates after daylight PDT did not differ from PDT using an LED illumination. Moreover, daylight PDT was less painful and 62% of the patients preferred daylight PDT. Further studies will show the effect of a pre-treatment with sun protection factor cream (SPF 20) prior to MAL application, to prevent sunburn during daylight exposure.

The Exhibition Hall and Poster Display in the Congress Centre.

The last talk of this session dealt with ambulatory light sources for PDT. **Dr Andrew McNeill** (Dundee, United Kingdom) presented an interesting new alternative of wearable light sources for use in PDT. This light source emits a low irradiance light and is applied at the same time as the photosensitiser. After 3 hours of incubation, the light source can be activated by the patient. Preliminary data show that it is as effective as existing light sources. Additionally, the low irradiance of the light source has been very well tolerated; almost without pain. Such a device could further simplify PDT and also improve tolerability.

The second plenary session focused on PDT in non-melanoma skin cancer (NMSC) and was chaired by **Prof Rolf-Markus Szeimies** (Recklinghausen, Germany) and **Prof Nicole Basset-Seguin** (Paris, France.). Firstly, **Prof Alexis Sidoroff** (Innsbruck, Austria) convincingly pointed out the need for a change in treatment approaches for NMSC. Since AK shows the same molecular changes as squamous cell carcinoma and many patients suffer from field cancerisation, macroscopic targeting of the lesions (e.g.

The Euro-PDT board (from left): Alexis Sidoroff (Treasurer), Lasse Braathen (President), Colin Morton (Secretary) and Rolf-Markus Szeimies (Vice-President).

with cryotherapy) is inefficient. Patients with a field disease profit from use of a field therapy, such as topical 5-FU, imiquimod and/or PDT.

Prof Basset-Seguin reported on PDT for superficial and nodular basal cell carcinoma (BCC). Recent studies looked at the efficacy of MAL-PDT for the treatment of nodular and superficial BCC. For nodular BCC, a randomised study comparing MAL-PDT (2 sessions, 7 days apart) with surgery in 101 patients with nodular BCC has reported a similar immediate response at three months and a recurrence rate at 5 years of 14% for MAL-PDT, compared to 4% with surgery. However, the higher recurrence rate with PDT was acceptable, as cosmetic outcome was significantly better in the PDT group. A similar 5-year follow-up study compared PDT with cryotherapy for the treatment of superficial BCC, showing similar complete response rates at 3 months (97% for MAL PDT and 95% for cryotherapy) and at 5 years (75% for MAL PDT and 74% for cryotherapy). Cosmetic results were much better for PDT.

PDT is particularly indicated for superficial and multiple BCC lesions – e.g in Gorlin's syndrome. **Dr Ernest Allan** (Manchester, United Kingdom) reported that BCC in Gorlin's syndrome responded to PDT as well as sporadic BCCs respond to this treatment. For small and superficial BCC, Metvix® PDT produced an excellent result. However, for thick and extensive lesions, a systemic photosensitiser (e.g. Photofrin®) was recommended. **Dr Christophe Bedane** (Limoges, France) reported excellent results using MAL-PDT in 22 patients with 38 cases of Bowen's disease. The remission rate was 100% at 6 months, 95% at 12 months and 85% at 24 months. This study confirms the good efficacy of PDT, which also enables easier treatment of large and multiple lesions than surgery.

PDT is not only effective in the treatment of epithelial tumours, but also in cutaneous lymphoma. **Dr Robert E Hunger** (Bern, Switzerland) presented the results of 4 case study series with 20 patients and 26 lesions of mycosis fungoides. The overall response rate after PDT was 70%. Six patients with 9 lesions were treated in his clinic and showed a complete response of 67%. No recurrence was observed in the follow-up period of 6-51 months, although some of the patients developed new lesions at other sites. The data on PDT of cutaneous B cell lymphomas have been very limited up to now. A case study series with 3 patients suffering from indolent cutaneous B cell lymphoma reported a complete response for all 4 lesions treated with PDT. Thus, PDT might be a therapy option in patients with single or few lesions of mycosis fungoides and probably also in patients with indolent cutaneous B cell lymphoma.

A very interesting new approach to improve the efficacy of PDT by a two-fold illumination scheme was presented by **Dr Ellen de Haas** (Rotterdam, The Netherlands). Preclinical and clinical studies show that ALA-PDT using a fractionated illumination scheme results in a significant increase in efficacy. In superficial BCC, response rates were significantly higher with fractionated ALA-PDT compared to a single illumination after a 1-year follow-up (97% versus 86%). A 5-year follow-up is underway. However, in a preclinical study using a fractionated MAL-PDT regimen, the efficacy was not enhanced. This may indicate that the mechanism of ALA-PDT is not the same as that of MAL-PDT.

Field Cancerisation was the topic of the 3rd Plenary session, chaired by **Dr Christophe Bedane** and **Dr Günther Hofbauer**

A view from a room in the Hotel.

(Zurich, Switzerland). **Dr Rianne Gerritsen** (Nijmegen, The Netherlands) gave a current overview on her group's studies on fluorescence diagnostics for detection of field cancerisation. They investigated different stages of AK, comparing fluorescence with histopathology. They were not able to differentiate between high- and low-risk AK. The thickness of stratum corneum seemed to be of great importance in fluorescence intensity. The intrinsic capabilities of different tissues to accumulate PpIX without interference of the stratum corneum were also studied in vitro and in vivo. **Prof Ann-Marie Wennberg** (Gothenburg, Sweden) talked more specifically about the problem of field cancerisation, a term that was recently introduced to describe those areas with an overt premalignancy which may also include areas of subclinical premalignancy. Since surgery or cryosurgery are not suitable to treat such large areas, treatment modalities such as 5-FU, imiquimod and PDT should be preferred. PDT has the advantage over the other topical treatments that it is 'one-shot' therapy, minimising the problem of patient compliance.

Multiple AK may also be located not only in the face, but also on the extremities. **Dr Colin Morton** (Stirling United Kingdom) addressed the dilemma of a relatively poorer response of acral AK to PDT as compared to facial sites. This could be related to a higher proportion of thicker lesions, to temperature issues or to a poorer drug absorption in the absence of pilosebaceous units. Nevertheless, PDT for acral AK has been observed to achieve superior cosmesis to cryotherapy, although efficacy rates were 10% inferior. PDT also appeared to be superior to topical imiquimod for acral AK. Although PDT is not licensed for non-facial AK (while for Bowen's disease or BCC there is no site specificity for the licensed use), PDT remains a useful option for multiple non-facial AK. To improve efficacy, a combination therapy or proportionately more treatments may be required.

Congress Dinner venue: the Cafe de Paris in Monte Carlo.

The 4th Plenary session focused on PDT for organ transplant recipients (OTR) and was chaired by **Prof Ann-Marie Wennberg** and **Dr Hans Christian Wulf**. **Dr Claas Ulrich** (Berlin, Germany) talked about the use of PDT in OTR, who often suffer from NMSC. Early diagnosis and therapy of pre-malignant skin tumours is crucial for these patients, to prevent development of invasive and aggressive skin cancer. PDT is a useful and efficient tool for the treatment of AK or BCC in OTR patients, although no standardised protocols are available for these high-risk patients as yet. **Dr Per Helsing** (Oslo, Norway) reported on his experiences with OTR patients in a 'real life' situation, because often patients in clinical studies do better than patients treated outside the trial environment. He established a system for quality surveillance of treatment in daily practice, with efficiency as an end-point, and could show that results after MAL-PDT of NMSC in OTR in a clinical setting are similar to the results published in clinical trials. **Dr Günther Hofbauer** then focused on some practical aspects of PDT in OTR. The main points in practical PDT application consist of removal of hyperkeratosis, choice of adequate field size, control of treatment effect by fluorescence dynamic diagnosis and repeated application until the disease is cleared. Since the effect of PDT in OTR appears to last less long than in the general population, a repetition of PDT every 6 to 12 months may be needed. He also reported on some rare complications observed after PDT in immunosuppressed OTR patients, such as reactivation of herpes virus or herpes zoster.

The French experience with PDT in OTR was presented by **Dr Nicolas Meyer** (Toulouse, France). Approximately 80 OTR with either AK or NMSC have been treated with MAL-PDT each year in his unit since 2007. About 70% of AK show complete response after 1 or 2 sessions of MAL-PDT, with good cosmetic outcome. Pain during PDT does not differ between OTR AK and 'normal' AK.

The last plenary session of the day had a very practical theme by asking colleagues from Europe how they perform PDT. **Dr Max Murison** (Swansea, UK) combined an UltraPulse CO_2 laser with MAL-PDT for the treatment of BCC, showing minimal recurrence rates after a follow-up of up to 5 years. **Dr Jacques Savary** (Paris, France) reported on his personal experiences with PDT in private practice. **Dr Sandra Campbell** (Truro, UK) demonstrated a novel method of enhancing penetration of MAL into nodular BCC, using an oxygen pressure injection device. **Dr Dario Fai** (Gagliano del Capo, Italy) presented his excellent results after MAL-PDT for actinic cheilitis in 26 patients. **Mr John Lear** (Salford, UK) treated 3 patients with giant BCC sequentially with 3 cycles of MAL-PDT followed by a 6-week course of topical imiquimod. This therapy led to a reduction in the size of the tumours which then could be excised. **Dr Pablo de la Cueva** (Madrid, Spain) evaluated the therapeutic effect of PDT on vulvar lichen sclerosus and vulvar intraepithelial neoplasia (VIP). A case of a patient with extramammary Paget's disease on the genital area (successfully treated with sequential PDT and imiquimod) was presented by **Dr B Leroy** (Brussels, Belgium). **Prof Alison Curnow** (Truro, UK) described a validated, non-invasive, fluorescence imaging system that permits understanding of PpIX changes within skin lesions during PDT. Such a device could help to improve clinical practice.

After these interesting and excellent talks, the Congress attendees could enjoy a nice evening at the Cafe de Paris in Monte Carlo, where the Congress Dinner took place.

SATURDAY, 13th MARCH

The first plenary session, chaired by **Prof Alexis Sidoroff** (Innsbruck, Austria) and **Prof Celeste Brito** (Braga, Portugal), focused on the non-oncologic indications for PDT. In the first talk, **Prof Sigrid Karrer** (Regensburg, Germany) gave an overview of the non-oncologic indications that have been studied in large randomised studies as well as in case study series or in single case reports. **Dr Bibiana Perez Garcia** (Madrid, Spain) reported on her non-oncological hospital-based PDT experience. Good results were achieved in acne and Hailey-Hailey disease. Actinic porokeratosis, psoriasis, alopecia areata, vitiligo, morphoea, keloids, syringomas, necrobiosis lipoidica, discoid lupus erythematodes or naevus sebaceous studied in a few patients did not show convincing results after PDT. **Dr Lesley Rhodes** (Manchester, United Kingdom) reported on the new developments in antibacterial PDT. Photosensitisers are able to bind to multiple sites within target cells and to destroy them by relatively non-specific oxidative damage. Thus, the likelihood of developing resistance is reduced. New photosensitisers are used for antibacterial PDT, such as cationic photosensitisers, which show activity against Gram-negative bacteria. Recently, clinical trials in patients with bacterially colonised leg ulcers and diabetic foot ulcers have been performed and show a significant reduction of germs in these wounds after PDT. In the future, probably also infected burn wounds, fungal infections, impetigo contagiosa or atopic dermatitis could be effectively treated by antibacterial PDT.

Prof Piergiacomo Calzavara-Pinton (Brescia, Italy) gave an excellent overview of PDT for acne and rosacea. Several studies report significant improvement of acne vulgaris, with long-lasting reduction of inflammatory lesions after an initial flare. However, there is potential risk of intense pain and oedema, erythema, crusting, and dyspigmentation. Treatments using intense pulsed visible light after short time sensitisation led to an improvement of inflammatory acne, with a reduction of short-term adverse effects and an enhanced tolerability. **Dr Stefano Piaserico** (Padova, Italy) presented data on PDT of granulomatous skin diseases. Granuloma annulare, cutaneous sarcoidosis and necrobiosis lipoidica have been successfully treated with PDT. The exact mechanisms underlying the positive response to PDT however are not yet understood.

PDT in Aesthetic Dermatology was the topic of the next plenary session, chaired by **Dr John Paoli** (Gothenburg, Sweden) and **Dr Bibiana Perez Garcia**. **Prof Rolf-Markus Szeimies** gave a mechanistic insight into the effects of PDT that might induce skin rejuvenation. Immunohistochemical analysis revealed upregulation of collagen production and increased epidermal proliferation. Neocollagenesis, as an indirect

dermal effect of PDT, is stimulated through cytokine induction.

Light sources that are used for aesthetic PDT were presented by **Dr Peter Bjerring** (Risskov, Denmark). New small lasers, LED sources and IPLs are currently being developed for aesthetic light treatment.

Dr Lorea Bagazgoitia (Madrid, Spain) analysed skin biopsies of patients with NMSC before and after PDT. Microarray analysis and immunohistochemical analysis of the samples were performed. Six weeks after PDT, a reduction of Ki-67 (a marker for proliferative activity) and p53 (important for the prevention of cancer) and an increase of COX-2 (usually upregulated in cancer) could be shown.

The last session of the Congress asked the provocative question 'No pain – No gain?' and was chaired by **Dr Pierre Thomas** (Paris, France) and **Prof Piergiacomo Calzavara-Pinton**. Pain is the major problem of PDT when treating large areas of AK or field cancerisation on the face and scalp. **Dr John Paoli** presented data from controlled clinical trials using nerve blocks to avoid pain during PDT. In two split-face studies, nerve blocks significantly reduced pain during PDT, were well tolerated and did not affect the therapy outcome. **Dr Eduardo Nagore** (Valencia, Spain) reported his experience with nerve blocks for PDT. His group could show that supratrochlear and supraorbital nerve blocks were significantly superior to cold air in patients with multiple AK. The last talk of the Congress was given by **Dr Julia Steinbauer** (Regensburg, Germany), who presented the data of comparative studies looking at pain and phototoxic reactions after PDT with either ALA or MAL. In a retrospective study in patients with AK or BCC on different body areas receiving ALA or MAL-PDT, factors predictive for higher pain levels could be determined: treatment of the head and scalp, AK as the treatment lesion and using ALA as photosensitiser. In another study, MAL-PDT and ALA-PDT were compared in healthy volunteers, showing stronger phototoxic skin reactions in the ALA-PDT group.

After the last talk, the prizes for the best posters and best presentations were awarded by **Prof Lasse R Braathen**. He then closed this very successful and well attended meeting.

It has subsequently been announced that the 2011 Euro-PDT Congress will take place in Paris, on March 11th and 12th.

Euro-PDT 2010: Poster Section, First Prize

Photodynamic diagnosis and therapy with Chlorin e6 – pathways, degradation and enrichment

Dirk Hüttenberger[1], Othmar Dill[2], Regina Bruce-Micah[1], Stephan Hassler[3], Hans-Jochen Foth[4], Carsten Philipp[5], Uwe Reinhold[6], Manfred Haupt[1]

1) Apocare Pharma GmbH, Bielefeld, Germany
2) Target GmbH, Worms, Germany
3) Harlan, Basle, Switzerland
4) University of Kaiserslautern, Germany
5) Elisabeth Hospital Berlin, Germany
6) Medical Center Bonn, Germany

The green porphyrin Chlorin e6 is known as a highly effective photosensitiser for systemic PDT. In preclinical animal studies and single case studies in patients, the tissue distribution and depletion kinetics of Chlorin e6 and its photodynamic potential were monitored. In a unique process of purification, it is possible to produce a chlorin as a pure, highly water-soluble sodium salt.

As part of our preclinical studies, the phamacokinetics were monitored by measurements with radioactive tritium-labelled chlorin. The material with a specific activity of 138kBq/mg was administered (50mg/kg bw) intravenously to mice. The concentrations of radioactivity in tissues and organs were determined by means of a quantitative whole-body autoradiography technique. The fluorescence was monitored using 2D-resolved fluorescence spectroscopy.

The animals were sacrificed 5 minutes and 3 hours after administration. The animals were frozen in a mixture of hexane/dry ice and embedded. Whole-body sections were taken at three levels of interest. The whole-body sections were exposed to imaging plates and the concentrations of radioactivity were determined by integration of the corresponding regions of the radioluminogram. The sections were then illuminated with blue light (410nm) to compare the fluorescence with the signal of the tritium-labelled material.

It should be noted that the applied dose level was approximately 100-fold higher than the proposed therapeutic dose. In the bile area, a high amount of radioactive-labelled material is present, but a decreasing fluorescence over time showed that a lot of labelled material is excreted over the hepatobilary tract, showing no fluorescence, indicating that there are only metabolites left, but no intact chlorin molecules.

In another study, the plasma level of Chlorin e6 was monitored with liquid chromatography. Eight hours after administration, it was shown that the Chlorin e6 level was lower than the detection level. In summary, we can assume that the degradation over the hepatobilary pathway plays an elementary role in a fast decomposition of the material in the body and leads to a short half-life in the plasma.

In some single case studies, the extremely well tolerated material was given to patients with Bowen's disease and basal cell carcinoma. All patients were treated with a Chlorin e6 dose of 0.8mg/kg bw. Three hours after administration, the illumination of the lesions was performed with a 662nm diode laser. The enrichment of chlorin in the lesions and surrounding tissues was measured with a fibreoptic spectrometer system during illumination with a 410nm LED light source.

One 48 year-old patient with Bowen's disease at the glans penis was treated (after prepuce resection and recurring lesions) with a light dose of 144J/cm^2. One day after illumination, a clear demarcation of the treated area was seen. The tumour-to-tissue ratio 3 hours after administration was approximately 7:1 (in comparison to the surrounding tissue). The plasma level of Chlorin e6 was measured continuously and, after 24 hours, the amount was lower than the detection level (see **Figure 1**).

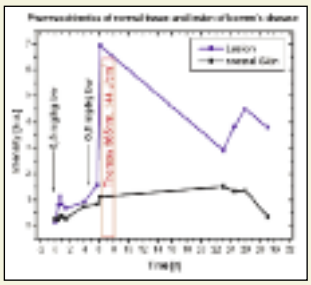

Figure 1: Characteristics of the fluorescence signal after systemic administration in a morbus Bowen lesion and normal tissue.

In two other cases, patients with basalioma were treated (nodular basaliomas behind the ear and on the nose). In both cases recurring lesions after resection and ALA-PDT were treated. The tumour-to-tissue ratio was up to 12:1 (see **Figure 2**). In both cases, the therapeutic effect after 60J/cm^2 (ear) and 33J/cm^2 (nose) was excellent and showed no recurrence after one year.

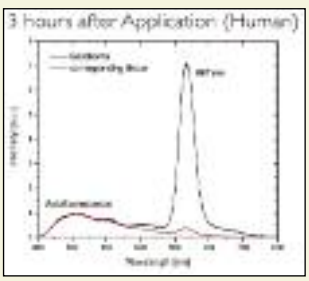

Figure 2: Tumour to tissue ratio in basalioma behind the ear versus the corresponding tissue of the other ear.

Euro-PDT 2010: Poster Section, 2nd Prize

Skin cancer preventive ALA-PDT for face and scalp field cancerisation

Elena Sotiriou

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Patients with a previous medical history of non-melanoma skin cancers (NMSCs) often develop multiple or recurrent malignant lesions around the site of the primary tumour. This finding led to the field cancerisation theory, which suggests that the entire epithelial surface of the regional skin has an increased risk of development of malignant lesions.

We sought to investigate whether field-PDT of extreme photo-damaged skin would prevent new NMSCs, in comparison to a control area receiving placebo-PDT, in patients with clinical and histological signs of field cancerisation.

Forty-five patients, previously diagnosed with NMSCs of face or scalp, with actinic keratoses (AKs) symmetrically distributed over the same regions, were randomised for field treatment with 20% ALA-PDT on one side and placebo-PDT on the other. Apparently normal skin of both affected areas was biopsied before the enrolment, in order to confirm the clinical diagnosis of field cancerisation. At baseline, all patients were clinically evaluated and photographed.

Both treatments were administered at baseline and at week 1. Photosensitiser (20% 5-ALA preparation, MEDAC GmBh Hamburg) was applied, covering a circular 50cm^2 field in one site, while only the vehicle cream was used as a 'photosensitiser' over the control field. After 3.5 hours of light-impenetrable occlusion, both areas were illuminated at a dose of 75J/cm^2 and irradiance of 75mW/cm^2 using a red light source (570-670nm, Waldmann PDT 1200, Waldmann-Medizin-Technik, Villingen-Schwenningen, Germany).

Follow-up visits were scheduled at months 3, 6, 9 and 12. During follow-up, only new clinically present lesions of both treatment areas were counted and recorded. Initial lesions were not recorded, even if they had not completely cleared.

Statistical analysis was performed using a two-sided Wilcoxon paired samples test. Mean time to occurrence of lesions was assessed with 95% Confidence Intervals (CI).

Overall, 39 patients (30 male, 9 female) completed the study. Ages ranged between 45 and 84 years (mean ± 68.92, SD ± 9.56). Selected areas were mainly located on the face (61.5%, 24/39) and less on the scalp (38.4, 15/39). Total numbers of new lesions, occurring during the intervals from baseline until each time point of follow-up, over both fields were statistically analysed. The results are summarised in **Table I**. Patients free of new lesions over both fields at each time point are reported in **Table 2**.

Table 1: Total number of new lesions at each follow-up on both fields and statistical analysis.

Follow-up time points (months)	Total no. of new lesions on PDT field	Total no. of new lesions on control field	p value, z
3	1	8	0.020, -2.333
6	2	15	0.001, -3.357
9	7	23	< 0.001, -3.771
12	14	30	< 0.001, -3.578

Significance level: $p < 0.05$, p represents the difference between total no of lesions on PDT field and on control field at months 3, 6, 9, 12.

Table 2: Subjects remaining free of new lesions at the treatment fields compared to the control fields, during follow-up.

Follow-up (months)	Patients free of lesions at 5-ALA PDT field	Patients free of lesions at placebo PDT field
3	38/39 (97%)	31/39 (79.5%)
6	37/39 (95%)	24/39 (61.5%)
9	32/39 (82%)	16/39 (41%)
12	25/39 (64.1%)	10/39 (25.6%)

Although not statistically significant, the number of new AKs developing in the control field during the third trimester was almost two times higher than the one observed in the PDT field (5 and 8 lesions, respectively). Fourteen of 39 individuals developed new AKs in the treatment field, and the mean time to occurrence of a new skin lesion was 9.86 months (SD: 2.74, 95% CI, 8.42-11.29). Correspondingly, 29 of 39 patients developed new lesions over the control fields, with a mean time to occurrence of 7.14 months (SD: 3.35, 95% CI, 5.92-8.36).

In conclusion, our encouraging results indicate that field PDT prevents the development of new NMSCs, especially AKs, and thus can be considered as an effective prophylactic strategy in patients with signs of field cancerisation.

Euro-PDT 2010: Selected Prize-Winning Oral Presentations

Markers of skin changes and prevention of NMSC

Lorea Bagazgoitia, MD
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Non-melanoma skin cancer (NMSC) is the most frequent cancer in the human being. It is in fact probably underreported due to its low mortality[1]. PDT has been shown to be effective in treating basal cell carcinoma, Bowen's disease and actinic keratosis (AK). Moreover, several studies, in both murine models and patients, have shown its effectiveness in prevention of NMSC[2-7]. This preventive effect is especially interesting for organ transplant recipients.

Our team is currently carrying out a multicentre research project, using cell cultures, in vivo models and studies in patients. In this setting, 70 hairless mice were divided into different groups: 20 mice received ultraviolet B (UVB) radiation periodically; 10 received UVB and MAL (Metvix®); 10 received UVB and red light; 20 were given both UVB and MAL-PDT; and 10 mice acted as a control group, which did not receive any treatment or irradiation. All the groups, except for the controls and the MAL-PDT group, developed several tumours on the irradiated areas. The gene expression profiling was identical in the control and the PDT groups.

Once the preventive effect of PDT was demonstrated in the murine model, the aim of the research activities in patients was to describe the changes in the pattern of expression of early markers of carcinogenesis after PDT and to evaluate their implication in the possible prevention of NMSC.

Twenty-two patients with biopsy-proven AKs were treated using MAL-PDT according to the standard protocols of our hospital. A new biopsy was performed 6 weeks after the treatment. The samples were stained for haematoxilin/eosin. In addition, immunohistochemical stains for Ki-67, p53, cyclin D1 and COX-2 were performed.

A reduction of basal keratinocytic dysplasia was observed, but it was not cleared in all the cases. Ki-67 and p53 expression were reduced after PDT, but expression of p53 did not disappear in every case. Cyclin D1 remained stable and COX-2 was slightly increased after treatment. The reduction of the basal dysplasia in the epidermis is consistent with what has been previously described in the literature, indicating that PDT is effective in clearing AKs[2,3]. However, a single treatment doesn't seem to be enough for a complete healing of the lesions. This has also been observed in several clinical trials.

The decreased expression of Ki-67, similar to that of the control skin after PDT, indicates that this therapy is able to reduce the proliferative activity of the skin. In addition, the reduction in the expression of p53, which is a well-known tumour suppressor protein involved in several human cancers, indicates the capacity of PDT to somehow reverse the carcinogenic process which can lead to a squamous cell carcinoma.

The fact that cyclin D1 expression, which is not commonly expressed in healthy skin, is not modified after treatment with MAL-PDT might be because one treatment is not enough. A clearance of this protein should be expected after more treatments.

COX-2 is an enzyme facultatively expressed where there is cancer-induced inflammation and is therefore not expressed in healthy skin. Surprisingly, its expression increased 6 weeks after MAL-PDT. This might indicate that PDT induces the activation of COX-2, which is involved in proliferation, angiogenesis and inhibition of apoptosis, favouring in some cases carcinogenesis[8]. The meaning of this effect is currently not well understood.

In conclusion, PDT not only reduces the proliferative activity of the epidermis, but also the expression of well-known markers of the skin oncogenic process, such as p53. A single treatment of PDT appears to be insufficient to achieve a complete clearance of the histological or the IHC markers in AK. Further studies are needed in order to fully understand the molecular mechanisms of PDT.

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PDT for actinic cheilitis

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Actinic cheilitis (AC) is a common premalignant condition which can progress into invasive squamous cell carcinoma. Effective treatment is therefore mandatory in order to minimise the risk of malignant transformation. Multiple treatment methods have been reported for AC, including cryosurgery, electrosurgery, carbon dioxide laser ablation, 5-fluorouracil, imiquimod or scalpel vermilionectomy, which are aimed at inducing destruction/removal of the damaged epithelium.

Recently, PDT has been introduced as a therapeutic modality for NMSC and AKs, with favourable efficacy/safety profiles and good cosmetic results. Preliminary reports have also proposed PDT as a new therapeutic approach to AC, which has also been confirmed by our personal experience, showing an excellent cosmetic outcome and a low relapse rate in the post-treatment period. Previous studes with topical PDT in AC are case reports and small case series. Here, we present our retrospective analysis of AC patients treated with MAL-PDT.

We performed a clinical diagnosis of AC in all cases and only 6 cases required histological confirmation.

Patients (n)	**26**	**Previous treatments for AC (n)**	
Males/females	18/8	Cryosurgery	15
Age, mean	71.7 yrs	Topical 5-fluorouracil	2
Age, range	53-88 yrs	Imiquimod cream	2
		None	7

MAL-PDT treatment details

- Application of MAL 160mg/g cream (Metvix®, Galderma)
  - 2 hrs in 23 pts
  - 3 hrs in 3 pts
- Exposure to red light (Aktilite CL 128, PhotoCure ASA, Oslo, Norway) at a fluence of 37J/cm^2
- Treatment sessions:
  - 1 single session in 4 pts
  - 2 sessions 1 week apart in 21 pts
  - 2 sessions at 1-week interval for 3 months (total= 6 sessions) in 1 pt

CLINICAL RESPONSE

- Complete remission: 18 pts (69.3%)
  - no relapse (follow-up period up to 24 months)
- Moderate to good improvement: 4 pts
- Poor/absent response: 3 pts
- Worsening: 1 pt

ADVERSE REACTIONS

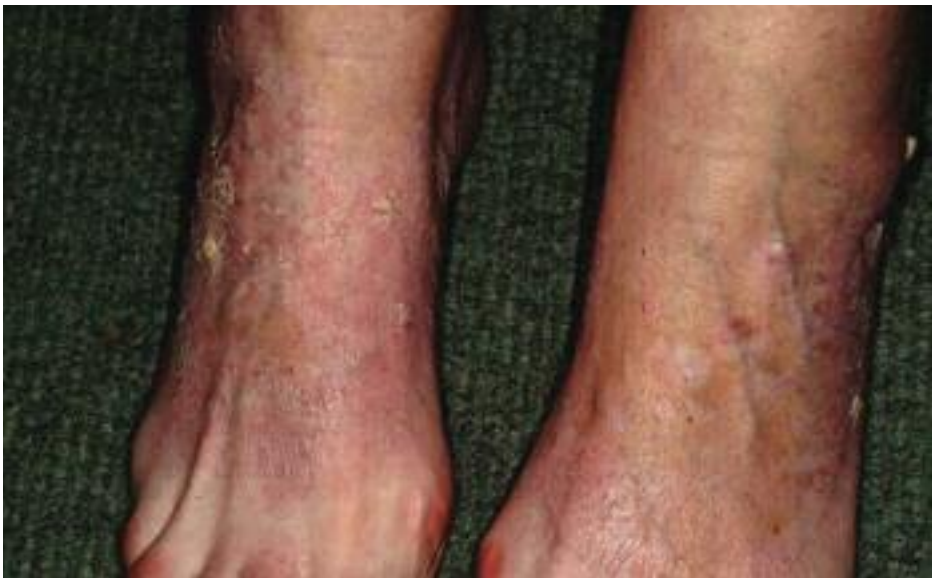
- Erythema: 21 pts (80.7%)
- Erosive/ulcerative lesions: 13 pts (50%)
  - remedies: emollient ointments; oral antiviral drugs in case of ulcers
- Pain/burning sensation in 23 pts (92.3%)
  - mild (tolerable) in 11 pts
  - moderate (requiring irradiation period to be split) in 9 pts
  - severe (requiring temporary discontinuation of illumination, application of cold dressings and air cooling) in 3 pts

COSMETIC OUTCOME

- Excellent results in 24 pts (92.3%)
- Scarring in 1 pt (3.8%)
- No dyschromic changes

PDT has a Place in the Treatment of Acral Skin Cancer

by: **Dr Colin Morton**
(Stirling, UK)



Multiple AKs on dorsum of feet.

Topical PDT is approved in many countries for the treatment of AK on the face and scalp, but there remains no licence for its use in acral AK, despite the prevalence of lesions on distal limbs. The impression from PDT practitioners has been of reduced efficacy when treating acral sites. Indeed, no fewer than 5 studies have indicated an inferior clearance rate of AK on the hands and arms compared to lesions on the face and scalp[1-5].Whilst clearance rates range from 71-98% for AK clearance on the head, the same studies indicated clearance rates ranging between 0-76% for acral sites – the difference is often because of duration of follow-up and significant differences in study design. In a more recent publication using MAL-PDT, Kaufmann *et al*[6] reported a multicentre, randomised, left/right comparison trial. Although a slight reduction in efficacy was observed with PDT (78% at week 24, compared to 88% for cryotherapy), there was superior cosmetic outcome reported following PDT. It is presumed that the relatively higher proportion of thick AK found on acral sites mitigate against achieving similar clearance rates to facial AK studies, despite the attempts of trial operators to exclude hyperkeratotic lesions. Although other theories exist that lower temperature might have an influence, or of inferior drug absorption at acral sites, differences in morphology of the lesions on acral sites appear a more likely explanation. Indeed, there is little evidence that acral location mitigates against efficacious PDT when we look at the literature concerning the clearance of Bowen's disease, given that over 75% of Bowen's lesions are located on the lower limbs.

Inferior response has been similarly observed with topical 5-fluorouracil (5-FU). In a comparison of ALA-PDT with topical 5-FU, Kurwa *et al*[7] showed an identical reduction in lesional area following a single cycle of each of these therapies and the author comments that historical studies observed that more intense treatment with topical 5-FU was necessary when treating acral sites.

Should a slight reduction in efficacy lead us to ignore PDT for acral actinic keratosis? I would argue, particularly in the light of the Kaufmann study, that we can achieve clearance of at least 75% of lesions on acral sites using PDT, using a hospital delivered high-compliance therapy with excellent cosmetic outcome, leaving remaining lesions to be treated by a local destructive therapy such as curettage or cryotherapy. Whether we will ever see a commercial licence for PDT in acral AK remains uncertain, but I would argue that the slight reduction in efficacy compared to cryotherapy should not dissuade us from considering MAL-PDT for acral AK. It is more difficult to interpret the early ALA-PDT literature, due to the lack of uniformity of protocol and of photosensitiser formulation.

In conclusion, topical PDT has a place for the treatment of acral AK, providing one accepts that the intention is to clear the majority of lesions and then undertake a focally destructive adjuvant therapy for the thicker, more hyperkeratotic lesions. Anecdotes and additional comments regarding readers' experiences of the use of PDT for non-facial AK are appreciated and will be published, space permitting, in future editions of ***Clinical Photodynamics***.

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Calendar of Events 2010

October 6-9, Brixen/Bressanone, Italy
8th International Symposium on PDT and Photodiagnosis in Clinical Practice
Contact: Prof Giulio Jori
Tel: +39 049827 6333
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e-mail: giulio.jori@unipd.it
Website: www.bio.unipd.it/2010-PDT

October 6-10, Gothenburg, Sweden
19th Congress of EADV
Contact: EADV Office
Tel: +322 650 0090 Fax: +322 650 0098
e-mail: office@eadv.org
Website: www.eadvgothenburg2010.org

December 9-12, Dresden, Germany
Cosmoderm XIV: European Society for Cosmetic and Aesthetic Dermatology
Contact: Isabelle Lärz
e-mail: cosmoderm2010@conventus.de
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