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Clinical Photodynamics

In Dermatology

An International Newsletter for PDT and FD in Clinical Practice

Editorial

Welcome to another issue of ***Clinical Photodynamics***. We feature reports on last year's EADO Meeting in Vienna and the EADV Congress in Berlin: the 2010 EADV will take place in Gothenburg (6-10 October).

We are also introducing a new feature – qualitative commentaries on recently published studies/case reports (see Pages 5-7). The intention is to draw attention to new publications in the field of skin PDT, especially from journals that we may not routinely read. Our hope is to interpret the significance of new studies, or suggest how new work sits within the established literature. We will include abstracts of the original publications, so readers can form their own views. The Editorial Board would welcome similar commentaries from readers, which we can publish in future issues, space permitting (please e-mail **eurocommunica@sky.com**). We hope this will herald a new, more interactive, phase in the activities of ***Clinical Photodynamics***. All published commentaries will be rewarded with a (small!) author's fee.

As we enter a new decade, my thoughts are also drawn to the place of PDT in our dermatological practice. Yes, we have many high-quality studies and evidence-based guidelines confirming efficacy (especially in actinic keratoses, Bowen's disease and basal cell carcinoma), but I still sense that PDT has yet to reach many patients who could greatly benefit from this therapy. Why? It remains frustrating how regulations vary between countries on the level of reimbursement for PDT, with costs to patients and viability to office practitioners being doubtless important in driving patient choice and therapy provision. Even where patients are fully covered, such as in the UK NHS, difficulties remain in providing an adequately staffed PDT service beyond regional centres. Although some clinician resistance remains, where understandable hesitancy exists in pursuing non-surgical therapies, I sense that our colleagues are becoming more reassured that non-surgical therapies have earned their place in the therapy 'options list' in non-melanoma skin cancer. More research to extend the indications for topical PDT is clearly required, yet funding for independent research is an increasing challenge.

As we approach the 21st 'birthday' of topical PDT, following Jim Kennedy's milestone publication in 1990, let's try to help introduce more patients to the benefits of PDT this year.

We will be carrying a report on the Monaco Euro-PDT Congress in the next issue – please feel free to e-mail (as above) your pictures/comments from this, 'The Big Event' in the PDT calendar.

Colin Morton, Stirling, UK

18th Annual Congress of the European Academy of Dermatology & Venereology

7-11 October, 2009 Berlin, Germany

by: **Prof Peter Foley**
(Melbourne, Australia)

WEDNESDAY 7th OCTOBER

EURO-PDT SUBSPECIALTY MEETING

On the first day of the EADV 2009 meeting in Berlin, the European Society for Photodynamic Therapy (Euro-PDT) held a sub-specialty/sister society meeting, hosted by the effervescent **Prof Lasse Braathen** (lately of Norway and Switzerland) and the steadfast **Prof-Dr Rolf-**

In this Issue

Markus Szeimies (Regensburg, Germany). This session provided a broad overview of PDT, with speakers from several European countries.

Author at the Berlin Wall, Potsdamer Platz.

PDT – A EUROPEAN EXPERIENCE

After Prof Braathen's welcoming address, the Euro-PDT Vice-President, the always engaging and thoroughly enjoyable **Prof Alexis Sidoroff** (Innsbruck, Austria), gave a presentation on 'Where PDT stands in 2009'. First and foremost, he emphasised that it is now well-established that PDT is effective in several therapeutic areas. Predominantly, it is used for the treatment of epithelial non-melanoma skin cancer. Prof Sidoroff contrasted the rigidity of randomised controlled trials with real-life experience. As he so eloquently pointed out in an analogy, the amputation of a limb will result in the 'cure' of superficial epithelial non-melanoma skin cancers in this limb, but the associated morbidity is somewhat excessive… Therefore, rather than concentrating purely on cure rates for these tumours when comparing therapeutic options, we should be looking at patient preference, cosmetic outcome, compliance, availability, practicality, primary costs of the treatment and secondary costs associated with review appointments, as well as other special considerations.

Prof Sidoroff also spoke briefly on the notion of fractionation of light dose. The concept behind the halting of illumination during treatment may allow the cells to reoxygenate and hence respond better to further illumination.

Pain associated with PDT seems to be a result of direct depolarisation of nerve fibres. Cooling of the skin, regional anaesthesia (nerve blocks) and the use of trans-cutaneous electrical nerve stimulation (TENS) machines all seem to be effective.

There are now a number of different ways of applying topical photosensitiser. Not only can we use the currently available preparations, but researchers are looking at different galenic formulations, micro- or nano-particles, liposomal preparations and ALA-impregnated patches.

Whilst light-emitting diode (LED) light sources appear to be the most frequently used means of delivering light, laser is also being utilised. Ambulatory PDT has been introduced and, due to photobleaching of the photosensitiser, there appears to be little risk of overdose. Sunlight has also been reported as a useful photosensitiser activator. Light-emitting tissues are also currently being evaluated.

Non-oncologic indications for PDT include the treatment of inflammatory, pilosebaceous, infectious and sclerotic or fibrotic conditions.

MAKING PDT WORK BETTER

Dr Maraia Nowakowska (Poland) then spoke on 'Nanostructural hybrid materials for PDT'. Whilst we tend to use porphyrins with excitation peaks in the visible light spectrum, including the Soret and the Q bands, porphyrins are large hydrophobic molecules that tend to aggregate in an aqueous environment. There is a lower efficacy of singlet oxygen production if porphyrins are aggregated. The ideal properties of a photosensitiser would be a hydrophilic and lipophilic hybrid with photochemical stability absorbing light from the visible light spectrum. Researchers have looked at the idea of attaching a porphyrin to a hydrophilic molecule and placing this in liposomes such as PEG gel. These agents look quite promising.

Dr Sandra Campbell (Truro, UK) examined the option of 'Enhancing PDT in non-melanoma skin cancer using iron chelating agents'. A number of iron chelators, including EDTA, DFO and CP94, have a low molecular weight and are directly absorbed into skin. They can be mixed with aminolevulinic acid (ALA) or methyl aminolevulinate (MAL: Metvix®) to enhance penetration. To date, studies with CP94 have shown enhanced fluorescence at standard timepoints for MAL and ALA, similar fluorescence at shorter timepoints and an increased response rate with nodular basal cell carcinomas (BCCs).

Prof Percy Lehmann (Wuppertal, Germany) discussed 'Hospital-based PDT in Germany'. Not surprisingly, the most commonly treated lesions were actinic keratoses (AKs), followed by Bowen's disease and superficial BCC. A small number of centres treat nodular BCC, human papilloma virus (HPV) infection and leishmaniasis

The Brandenburg Gate at Night. *© Eishier – Fotolia.com*

routinely. The majority of German centres responding to Dr Lehmann's survey use both MAL and ALA, with smaller numbers using exclusively MAL or ALA. The most common light source is the Aktilite with the smaller number of centres using a Waldman light source. Difficulties with insurance were variable across the survey with equal numbers of centres experiencing no difficulties, some difficulties or having to negotiate an agreement.

Dr Elena Sotiriou (Athens, Greece) compared PDT with imiquimod for the treatment of AKs in an intra-individual manner. Response rates were higher on the PDT-treated arm. Patient preference tended to favour PDT, with most participants indicating they would prefer PDT over imiquimod in the future.

Dr Marina Venturini (Brescia, Italy) presented data on in vivo reflectance confocal microscopy as a means of diagnosing BCC. This technique seems to be highly sensitive and specific, and was very accurate when compared to histological response – more so than clinical assessment or dermoscopic review.

Dr Annette Klein (Regensburg, Germany) spoke on enhancement of 5-ALA

One of the earliest adverts for a sun protection cream, dating from the 1930s

penetration in erbium:YAG laser-stripped stratum corneum. One J/cm^2 of erbium:YAG laser followed by a 3-hour incubation with ALA resulted in enhanced fluorescence. This may be a means of increasing the efficacy of PDT.

Dr Celeste Brito (Braga, Portugal) gave a status report on PDT in Portugal. Dr Brito's centre was the first to introduce PDT as a routine management for epithelial non-melanoma skin cancer in Portugal. She discussed the long experience of her unit.

The final speaker in the session, **Dr Denny Siem** (Leiden, The Netherlands), reported that disseminated superficial actinic porokeratosis, treated with ALA for 3-4 hours under occlusion, followed by illumination with the Omnilux lamp, and repeated every 4 weeks, seemed to result in clearance after 3 or 4 sessions. This is certainly better than what the literature has to date reported.

OTHER DAYS

PDT AT OTHER EADV SESSIONS

Additional presentations on PDT were given in the cutaneous oncology course, the melanoma and non-melanoma skin cancer free communications session, and a symposium shared with phototherapy. PDT was also the subject for the Intendis satellite symposium entitled 'New simplicity in PDT: Advantages in the treatment of AKs with a self-adhesive 5-ALA patch.' This development has been discussed in previous issues of ***Clinical Photodynamics***. In addition, a number of posters reporting on the use of PDT as a treatment modality were presented in both the non-melanoma skin cancer and photodermatology sections.

The future of photodynamic therapy looks bright. ■

Prime Time PDT

An international roundup of PDT-related papers and publications

Therapeutic Hotline: Facial skin rejuvenation in a patient treated with photodynamic therapy for actinic keratosis

Bruscino N, Rossi R, Dindelli M *et al* 2010 *Dermatol Ther* **23** 86-89

Although not the primary reason for PDT usage in dermatological lesions, the excellent cosmesis achievable with this modality continues to impress both clinicians and patients: this may prove to be a major factor in the wider adoption of PDT as a routine therapy. The key aspect of this Italian case study, strongly emphasised by the authors, is the skin rejuvenation effect achieved. An elderly man whose AK had proven to be resistant to other treatments was treated with MAL-PDT, not only resulting in removal of the lesion but also the surrounding wrinkles and 'ugly lines'. The smoothness of the skin was assessed and confirmed by a 3D profilometry technique.

Photodynamic therapy in dermatology

Steinbauer JM, Schreml S, Kohl EA *et al* 2010 *J Dtsch Dermatol Ges* Feb 3 [Epub ahead of print]

This German review of the current status of, and potential for, PDT will, no doubt, be widely cited in future PDT publications. Basic principles are explained, the current photosensitising agents and light sources are discussed, and the oncological and non-oncological uses of dermatological PDT are considered.

Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies

Foley P, Freeman M, Menter A *et al* 2009 *Int J Dermatol* **48** 1236-1245

Nodular basal cell carcinoma (nBCC) is currently a 'grey area' for routine use of PDT: however, studies continue to accumulate that include refinements in the treatment technique and show improved response rates. This Australian-based group report on two multicentre, randomised studies which compared MAL-PDT with placebo. A total of 131 patients with nBCC were randomised 1:1 to receive either MAL-PDT (consisting of surface debridement and minor debulking, with 3 hours of occlusion, followed by illumination at a dose of 75J/cm^2 from a broad-spectrum red light source), or the same regimen but with a placebo cream. Two treatments were given, 7 days apart. After 3 months, lesions

showing a partial response (≥ 50% reduction in greatest diameter) were retreated. The treatment sites were excised at 3 months after last treatment for clinical non-responders, or at 6 months post-final treatment for clinical responders. The histologically confirmed lesion complete response (CR) rates were 73% (55/75 lesions) for MAL-PDT, compared to 27% (20/75 lesions) for placebo. There was a CR rate of 89% for facial nBCC, and cosmetic outcome was good or excellent for 98% of evaluable CR lesions. The authors acknowledge that longer follow-up studies are required, but concluded that their results show the potential for MAL-PDT as a useful non-invasive treatment for nBCC.

Current and new treatments of photodamaged skin

Shamban AT 2009 *Facial Plast Surg* **25** 337-346

This evaluation of the options for treatment of photodamaged skin has been published in a journal which is likely to be unfamiliar to the majority of ***Clinical Photodynamics*** readers, but again emphasises the reality that PDT has expanded far beyond a strictly medical usage. In this paper, we learn that PDT (here used with 5-ALA) is the 'treatment of choice for type C photodamage'. The author describes how 'low-strength' (1-2%) 5-ALA is applied 'several times every 10-15 minutes', before incubation for 30-60 minutes with 550-630nm, 530-1200nm or 570-1200nm light activation. Improved hyperpigmented lesions, skin smoothing and skin elasticity have been reported, with a high degree of patient satisfaction. The author also describes the use of a 0.5% liposome-encapsulated 5-ALA spray, as an alternative to the 20% 5-ALA cream base.

Photorejuvenation with topical methyl aminolevulinate and red light: a randomized, prospective, clinical, histopathologic, and morphometric study

Issa MC, Piñeiro-Maceira J, Vieira MT *et al* 2009 *Dermatol Surg* [Epub ahead of print]

This Brazilian study used MAL-PDT for photorejuvenation in 14 patients, but also included histological and morphometric analysis of the end results, in addition to clinical visual evaluation. Two treatments of MAL-PDT were given: 10 patients were seen to have global clinical improvement, assessed by texture, firmness, wrinkle depth, skin colouration and clearance of AK. A histopathological examination found increased collagen fibres at 3 and 6 months after treatment, with a statistically significant decrease in elastic fibre at 3 months ($p = 0.016$) and 6 months ($p = 0.008$) post-treatment. The increase in amount of collagen fibre was also significant at 6 months ($p = 0.048$).

Successful photodynamic therapy with topical 5-aminolevulinic acid for five cases of cervical intraepithelial neoplasia

Wang J, Xu J, Chen J *et al* 2009 *Arch Gynecol Obstet* Dec 19 [Epub ahead of print]

A five-case study of patients with cervical intraepithelial neoplasia (CIN) and high-risk HPV infections were treated with 5-ALA gel (118mg/g) applied to the cervix, with occlusion with a special plastic cap for 3-4 hours, followed by illumination for 20 minutes with 630nm laser light via a special light catheter to both the ecto- and endo-cervical canal. Treatment was repeated 7 days later and the patients followed up at 3, 6 and 9 months post-treatment. All the patients with stage 2 CIN had a CR for the 9 months. One patient with stage 3 CIN was still HPV-positive for 6 months and received further PDT. The authors concluded that PDT offers a non-invasive and repeatable procedure, with minimal side-effects for these patients, and can be performed as an out-patient therapy.

Photodynamic therapy with topical methyl- and hexylaminolevulinate for prophylaxis and treatment of UV-induced SCC in hairless mice

Togsverd-Bo K, Lerche CM, Poulsen T *et al* 2010 *Exp Dermatol* Jan 21 [Epub ahead of print]

The search for photosensitisers that are effective in treating squamous cell carcinoma (SCC) continues. Hexyl aminolevulinate (HAL) is more lipophilic than MAL, so may be more easily absorbed into these lesions. This Danish-based study used a hairless mouse model to compare HAL- and MAL-PDT for UV-induced SCC. Three doses of HAL (2%, 6% and 20%) were compared to 20% MAL and placebo PDT. The mice were given 2 prophylactic PDT sessions, followed by 2 further treatments when the first developed SCC reached 1mm in size. The median time to development of SCC was significantly longer for mice that received either HAL- or MAL-PDT, compared to placebo ($P < 0.0001$). Therapeutic cure rates for either HAL- or MAL-PDT were 23-61.5% ($P = 0.11$). Although fluorescence rates were similar for both HAL- and MAL-treated animals, a more intense hyperpigmentation was seen in mice given 20% MAL, compared to those given 2% HAL.

A comparative study on the enhancement efficacy of specific and non-specific iron chelators for protoporphyrin IX production and photosensitization in HaCat cells

Xia Y, Huang Y, Lin L *et al* 2009 *J Huazhong Univ Sci Technolog Med Sci* **29** 765-770

Iron chelators have shown considerable promise for the improvement of PDT outcomes by their ability to block the conversion of PPIX to haem, thus allowing greater amounts of PPIX to accumulate in the target tissues. This in vitro study from Wuhan, China, directly compared two iron chelators, DFO and EDTA, using a culture of HaCat cells. The cells were incubated in darkness for 3 hours with 20mmol/l of ALA and either DFO or EDTA (with a control of ALA incubation alone), when the concentration of cellular PPIX was evaluated by high-performance liquid chromatography. Fluorescence emission at 630nm was also observed. To evaluate PDT, the cells were illuminated with 632.8nm laser light, with flow cytometry used to assay the proportions of apoptotic and necrotic cells. Both iron chelators gave higher results than for ALA alone: however, DFO (a specific chelator) had a greater potential for PDT enhancement than EDTA.

illuminating words

A new ***Clinical Photodynamics*** feature, where Board Members and Readers offer their qualitative commentaries on recently published papers of relevance to topical PDT. For clarity, the commentaries are printed in italics, with an accompanying short abstract of the selected paper(s) in roman script.

PDT and Prevention of Recurrence

Apalla Z, Sotiriou E, Chovarda E, Lefaki I, Devliotou-Panagiotidou D, Ioannides D 2010. Skin cancer: preventive photodynamic therapy in patients with scalp and face cancerization. A randomized placebo-controlled study. *Brit J Dermatol* **162** 171-175

This study extends our understanding of the preventative role of PDT in non-melanoma skin cancer (NMSC). Whilst previous studies have looked at organ transplant recipients, all patients in this study were systemically immunocompetent, with actinic keratoses (AK) against a background of severe photodamage. Selected areas on the face/scalp were randomly allocated to either ALA-PDT or placebo-PDT, using red light, repeated after 7 days. A significant delay in time of appearance and reduction in total number of new lesions occurred after active treatment. Of particular interest was the time-related gradual decline of prophylactic effect, with only 1 new lesion at 3 months, then 2 at 6 months, 7 at 9 months and 14 at 12 months following ALA-PDT, contrasting with 8, 15, 23, and 30 in identical-sized areas treated by placebo over the same follow-up intervals. This suggests that repeat intervention with field-PDT after 6-9 months could have maintained the low new lesion rate. Other authors have demonstrated red light MAL-PDT to be able to reduce new lesions in transplant recipients, although one study with violet light and ALA-PDT had failed to show a significant reduction in SCC. In my opinion, this study reminds us that immunocompetent patients can benefit from a preventative PDT regimen, and that we should strive to develop improved protocols that can make field-PDT more practical for routine clinical use.

Colin Morton

Apalla and colleagues, based in Thessaloniki, Greece, recruited 45 immunocompetent patients with previously diagnosed NMSC of the face or scalp, with AK evenly distributed over the same areas (field cancerisation). Target areas on both left and right sides were selected, the lesions present being carefully counted and mapped on anatomical diagrams. They were then randomly assigned to receive ALA-PDT (as a 20% cream, 1mm thick over a 50cm^2 diameter field, with 3.5 hours of occlusion prior to illumination with a Waldmann® PDT 1200 red light source at a dose of 75Jcm^2) to either the left or right side, with the placebo base cream being administered identically to the other as a control. The treatment was repeated one week later. The patients received advice on maximum protection sunscreens (SPF 50+) and avoidance of sun exposure.

A total of 39 patients (30 men: 9 women, mean age = 68.9 years) completed the study. All patients were clinically evaluated and photographed at baseline, then assessed blindly by the same physician at 3, 6, 9 and 12 months post-treatment, to avoid bias. Only new clinically present lesions (scales, erythema) were recorded. At 3 months, the treated fields showed 1 new lesion, compared with 8 lesions for the placebo fields ($P = 0.02$). Statistical significance ($p < 0.05$) was also maintained for the rest of the study period between the treated and placebo fields (as detailed in Dr Morton's comments, above). New lesions were seen in 14 of the treated fields, compared to 29 of the placebo fields. The mean time to recurrence was 9.86 (±2.74) months for treated areas, compared to 7.14 (±3.35) months for placebo areas. At 12 months, 25 (64%) of the patients remained recurrence-free in the treated fields, versus 10 (26%) patients with no recurrence in the placebo fields.

The authors concluded that field-PDT gives a significant preventative potential against new lesion formation in this patient group.

Predicting Pain in PDT

Virgili A, Osti F, Maranini C, Corazza M 2010. Photodynamic therapy: parameters predictive of pain. *Brit J Dermatol* **162** 460-461

The promise in the title – parameters predictive of pain - raised my hopes of clarity in this topic at last! Pain can be challenging to manage during PDT, with variation between patients, type, size and location of lesions, intensity of PDT reaction, etc. This latest study has also sought to investigate the relationship between pain and skin type, as well as pain severity relative to erythemal response. Patients with skin type III perceived more pain than those with type IV, but there was no correlation between pain and change in erythema. I was frustrated to note that this manuscript had been published without the inclusion of treatment protocol, making comparisons with previous studies impossible. Sadly, this short report has not answered my call for clarity. To be fair, despite the study size of 121 patients with 316 AK or 'carcinomas', the authors acknowledge that much larger studies are required, that may help clarify some of the contradictory published evidence on this topic.

Colin Morton

This short correspondence gives an outline of a study performed on 121 patients of Italian origin with Fitzpatrick skin types III or IV (total 316 lesions). Patients with skin type III developed more lesions (mainly AK) than those with skin type IV ($P = 0.04$). Unspecified PDT was administered and pain assessed on a visual analogue scale (VAS). Severe pain (VAS score 7-10) was recorded for 41.4% of patients, which the authors noted was much higher than in other published studies. Treatment of AK was assessed as more painful than treatment of carcinomas and was independent of age or number of lesions treated. Treatment of head and neck lesions was rated as more painful than those on the limbs and trunk ($P < 0.001$), but no significant difference between lesions on the limbs and trunk was seen ($P = 0.11$). Furthermore, no sex difference in pain perception was observed ($P < 0.1$), but patients with skin type III recorded significantly higher pain than those with skin type IV ($P < 0.04$). A subset of 73 lesions evaluated for erythema before and after PDT (erythema index [EI] via a DermaSpectrometer®) did not show any statistical significance between redness and level of pain. The authors also found no difference in pain levels between first and second PDT treatments. They discussed the differences seen in their study with other published studies and concluded that further multicentre international trials were required before effective guidelines on prediction of PDT-related pain could be drafted.

Nerve Blocks to Relieve Pain During PDT

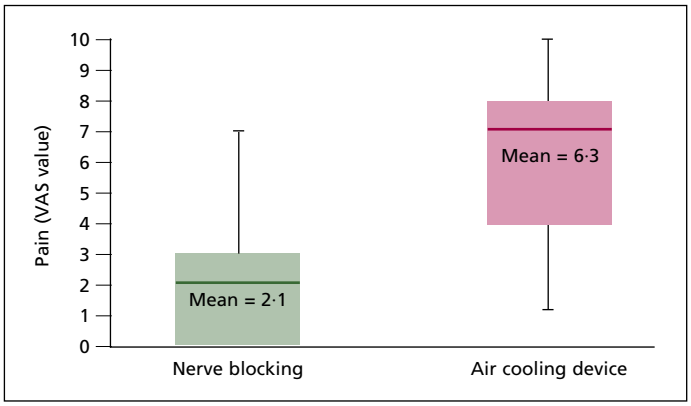
Halldin CB, Paoli J, Sandberg C, Gonzalez H, Wennberg AM 2009. Nerve blocks enable adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp. *Brit J Dermatol* **160** 795-800

Serra-Guillen C, Hueso L, Nagore E, Vila M, Llombart B, Requena Caballero C, Botella-Estrada R, Sanmartin O, Alfaro-Rubio A, Guillen C 2009. Comparative study between cold air analgesia and supraorbital and supratrochlear nerve block for the management of pain during photodynamic therapy for actinic keratoses of the frontotemporal zone. *Brit J Dermatol* **161** 353-356

Pain during PDT is the major drawback of this therapy, sometimes even requiring the interruption of irradiation and thus reducing the efficacy of PDT. After such a painful experience, patients also would probably refrain from PDT in the future, even if indicated. These two studies show a very effective and well-tolerated way to get rid of this side-effect and thus to improve patient satisfaction. The authors investigated the efficacy of a nerve block in a side-by-side comparison, with the aim of controlling pain during PDT for extensive AK and field cancerisation on the forehead and scalp.

Serra-Guillen et al *treated 34 patients with multiple AK in the frontotemporal region with MAL-PDT. On one side of the frontal region, the supratrochlear and supraorbital nerves were blocked using mepivacaine, compared to cold air on the other side. In the second study, Halldin* et al *treated ten men with extensive AK on the forehead and scalp with MAL-PDT. One side was anaesthetised by a combination of supraorbital/supratrochlear and occipipital nerve blocks using bupivacaine-adrenaline. The other side of the head served as a control: spraying of cold water was allowed on both sides if needed.*

Re-drawn Figure 2 from Serra-Guillen *et al* 2009



Re-drawn box plot for pain (visual analogue scale), to allow more direct comparison with Halldin *et al*. The box shows the upper and lower quartiles, with the median (horizontal line). The mean is included in each box.

In both studies, pain during PDT was documented on a visual analogue scale (VAS) directly after PDT. In both studies, pain was significantly less in the anaesthetised side, compared to the control side. In the Halldin et al *study, the VAS score during PDT was 1 ± 0.29 on the anaesthetised side, compared with 6.4 ± 0.82 on the control side, whilst Serra-Guillen* et al *reported a VAS score of 2.1 ± 2.2 on the anaesthetised side, compared with 6.3 ± 2.8 in the control group with cold air. These studies show that nerve blocks are an effective, easy and safe method to control pain associated with PDT.*

The issue of pain during PDT for extensive lesions has not yet been solved satisfactorily. Usually, cold air analgesia is used with often insufficient efficacy when treating larger areas. Topical anaesthetics or capsaicin cream have not proven to be useful. Since field cancerisation and multiple AK often involve the forehead and the scalp, nerve block provides effective anaesthesia over relatively large areas of the skin, needing only a small number of painful injections with the local anaesthetic.

Moreover, although pain is most intense during irradiation, it often also persists for several hours after the procedure. Halldin et al *contacted the patients by telephone within two weeks after PDT, to ask about the pain-relieving effect of the nerve block during the first few hours after PDT. The patients reported that they experienced mild to moderate pain after PDT only in the non-anaesthetised side. 80% of the patients were positive about receiving nerve blocks bilaterally, if PDT were required again in the future.*

This is also an important aspect of the nerve block: it not only controls severe pain during PDT, but also the mild to moderate pain that can last for hours after PDT is almost completely relieved. This might increase the patients' acceptance of this effective treatment and might also contribute to their willingness to undergo further PDT treatments in the future, if necessary.

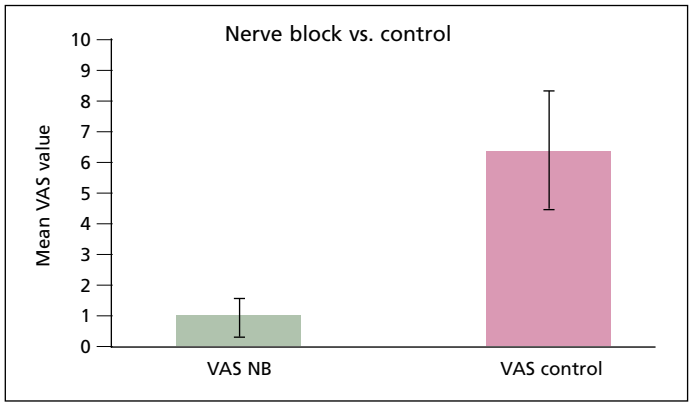
Sigrid Karrer

A Swedish study by Halldin and colleagues at the Sahlgrenska University Hospital, Göteborg (Gothenburg), recruited 10 men (mean age = 76 years) with extensive, symmetrically distributed AK and signs of field cancerisation on the forehead and scalp who had been prescribed PDT. The patients were randomised to receive local nerve-blocking anaesthesia (bupivacaine-adrenaline [Marcain®]) to either their left or right sides, administered at least 15 minutes prior to illumination to ensure good distribution.

The other side was left unblocked as a control. After light curettage, MAL (Metvix®)-PDT was administered (occlusion time 3 hours, illumination dose 37-45Jcm^2, using an Aktilite® CL 128 red light source) to the complete treatment area. At the patients' request, cold water was also sprayed to either side, to ensure that the only treatment variable was the nerve block. Pain was assessed separately for each treatment side directly after completion of irradiation, with the patient sliding the marker on the VAS ruler to the appropriate point on the scale (0 = no pain: 10 = unbearable pain). Patients were also contacted by telephone 2 weeks after treatment to assess their degree of post-treatment pain and report any adverse effects. All patients were followed up at 8-14 weeks for the clinical results of PDT.

The mean VAS score for the anaesthetised side was 1 ± 0.29, compared to 6.4 ± 0.82 for the non-anaesthetised side ($P < 0.0001$). One patient reported moderate bilateral pain for up to 48 hours post-PDT. Eight of the patients said that they would opt for bilateral nerve blocks if a future PDT was required: the other two patients

Re-drawn Figure 3 from Halldin *et al* 2009



The mean visual analogue scale (VAS) value on the side anaesthetised with nerve blocks (VAS NB) compared with the mean VAS value on the non-anaesthetised side (VAS control). Error bars indicate SEM.

considered that PDT was not painful enough to require anaesthesia. All patients showed a clearance rate of >75% of the treated areas, with no difference between the two sides.

Nerve blocking to one side was also used in the study by Serra-Guillen *et al* (Valencia, Spain). Here, topical anaesthesia with mepivacaine was compared to a stream of cold air (Zimmer cold air blower) in 34 patients (32 men: 2 women, median age = 75 years) with evenly distributed multiple AK/field cancerisation of the frontal or frontoparietal region. MAL-PDT was similar to the Halldin study (light curettage, 3 hours of occlusion, illumination dose of 75Jcm^2, using an Aktilite® red light source). After irradiation, the patients were asked to score their pain (0 = no pain: 10 = maximal pain imaginable) for each side of treatment. The patients were followed up at 24 hours, 1 week, 1 month and 3 months after PDT.

A significantly lower level of pain was recorded by 31 patients (91%) in the nerve-blocked area (mean VAS score 2.1 ± 2.2 for the nerve-blocked side versus 6.3 ± 2.8: $P < 0.001$), whilst 3 patients considered the levels of pain to be similar between the two sides. There were no clinical differences in clearance rates between the two treated sides. One year after treatment, 27 patients were contacted by telephone about their memory of the pain and preference for nerve-blocking anaesthesia for any future treatment: 7 patients could not recall their sensations during PDT, 5 patients expressed no preference and 15 said that they would prefer nerve-blocking anaesthesia. Interestingly, all 5 patients who expressed no preference had shown smaller differences (< 3 points) in their perception of pain between cold air and nerve block. There was a slight, non-significant, trend for younger patients (≤ 75 years) to prefer nerve block.

5th Congress of the European Association of Dermato-Oncology (EADO)

12-16 May, 2009, Vienna, Austria

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

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The 5th Congress of the EADO was a combined meeting with the 7th World Congress on Melanoma. PDT was debated in two of the main sessions. In the first session, **Professor Rolf-Markus Szeimies** (Regensburg, Germany) covered mechanisms of action, **Professor Lasse Braathen** (Bern, Switzerland) discussed current and future PDT procedures, **Dr Sonja Radakovic** (Vienna, Austria) reviewed its role in dermatological oncology, and **Professor Herbert Hönigsmann** (Vienna, Austria) reviewed potential side-effects. In addition to reaffirming efficacy, the presentations considered the importance of some recent publications. Professor Braathen considered that, while methyl aminolevulinate (MAL: Metvix®)-PDT is currently licensed to have a three-hour incubation before illumination, a recent study has concluded that one hour may be sufficient for treating particularly thin and moderate thickness actinic keratosis (AK) with limited loss of efficacy from the reduced incubation time.

Several posters also referred to PDT and included two reviewing efficacy and cosmetic results of a novel 5-ALA patch in topical PDT. In a study by **Professor Axel Hauschild *et al*** (Kiel, Germany), twelve week complete clearance with ALA-PDT using the patch was 82%, whilst in a comparison study of PDT using the patch compared with cryotherapy, **Professor Szeimies *et al*** reported complete clearance on a lesion basis of 89% with PDT versus 77% by cryotherapy. **Dr S Schreml *et al*** (Regensburg, Germany) presented a comparison of phototoxic reactions following MAL- or ALA-PDT. Thirty-four healthy volunteers were treated by PDT with the photosensitiser used randomly assigned to treatment areas on the inside of each upper arm. A composite score of local phototoxic events (erythema, oedema, hyperpigmentation) was calculated and pain measured using a visual analogue scale. MAL- and ALA-PDT were nearly equivalent regarding individual side-effect frequencies, but MAL-PDT had a more favourable phototoxicity pattern on area under the curve analysis and a lower frequency of longstanding hyperpigmentation. In a further study presented by the same group, attempts were made to precisely assess how reported pain during PDT may be predicted by gender, age, treatment site, the type of lesion and photosensitiser used. The results indicated that higher pain was successfully predicted when: ALA- rather than MAL-PDT was used; lesions treated were on the head; and treatment of AK (versus BCC). Primary treatments were noted to be significantly more painful, compared with follow-up treatments, but gender and age did not contribute significantly to the influence on pain reported.

Drs Diona Damian and **Y Matthews** (Sydney, Australia) reported on the immunosuppressive effects of topical PDT in humans. Healthy Mantoux-positive volunteers had discrete areas of normal skin on their lower backs illuminated with a narrow red light source with and without prior application of the photosensitisers (either ALA or MAL). Adjacent untreated and non-irradiated areas of skin served as immunologically intact control sites. Delayed hypersensitivity responses to tuberculin purified protein derivative were then elicited in each of the sites. The intensity of the Mantoux reactions at each site was then measured and it was observed that MAL- and ALA-PDT caused significant immunosuppression of between 30–80%. Red light alone, even without photosensitiser, also significantly suppressed the Mantoux reaction. The authors hypothesised that PDT-induced immunosuppression could be a factor in actually impairing local anti-tumour immune responses and might be a contributor to treatment failure in certain cases. The full abstracts for the above presentations are still available to view at:

www.worldmelanoma2009.com.

Calendar of Events 2010

April 7-10, Madrid, Spain
13th World Congress on Cancers of the Skin
Contact: WCCS Congress Organiser
Tel: +34 690 846 097
Fax: +34 932 057 230
e-mail: sbc@sbc-congresos.com

April 8-10, Monte Carlo, Monaco
8th Anti-Aging Medicine World Congress
Contact: AMWC 2010 Congress Secretariat
e-mail: amwc@antiageingevents.net

April 14-18, Phoenix, USA
Annual Conference of the American Society for Laser Medicine and Surgery
Contact: American Society for Laser Medicine and Surgery
2100 Stewart Avenue, Suite 240, Wausau, WI 54401, USA
Tel: +1 715 845 9283
Fax: +1 715 848 2493
e-mail: information@aslms.org

April 21-25, Rio De Janeiro, Brazil
22nd Brazilian Congress of Dermatologic Surgery
Contact: Milena Xavier
Tel: +55 17 3235 7017
Fax: +55 17 3235 5334
e-mail: cenacon@cenacon.com.br

April 22-28, Washington DC, USA
Annual Meeting of the American Society for Aesthetic Plastic Surgery
Contact: ASAPS Congress Organiser
Tel: +1 800 364 2147
Fax: +1 562 799 1098
e-mail: asaps@surgery.org

May 13-16, Cavtat/Dubrovnik, Croatia
7th EADV Spring Symposium
Contact: Mrs Jelena Krmic
Tel: +385 1 4862 600
Fax: +385 1 4862 622
e-mail: info@eadvcavtat2010.com

May 20-22, Lausanne, Switzerland
10th Congress of the European Society for Paediatric Dermatology
Contact: ESPD Congress Secretariat
Tel: +41 223 399 571
Fax: +41 223 399 631
e-mail: espd2010@mci-group.com

June 16-19, Athens, Greece
6th Congress of the European Association of Dermatologic Oncology
Contact: Mrs Penelope Mitroyianni
Tel: +30 210 725 7693
Fax: +30 210 725 7532
e-mail: info@eado2010.org

September 9-11, Helsinki, Finland
40th Annual Meeting of the European Society for Dermatological Research (ESDR)
Contact: ESDR Congress Secretariat
Tel: +41 22 321 4890
Fax: +41 22 321 4892

October 6-10, Gothenburg, Sweden
19th Congress of the European Academy of Dermatology and Venereology (EADV)
Contact: EADV Office
Tel: +322 650 0090
Fax: +322 650 0098
e-mail: office@eadv.org
Website: www.eadvgothenburg2010.org
DEADLINE FOR EARLY BIRD REGISTRATION: 18 JUNE

December 9-12, Dresden, Germany
Cosmoderm XIV: International Aesthetic Dermatology Congress of the European Society for Cosmetic and Aesthetic Dermatology
Contact: Isabelle Lärz
Tel: +49 3641 3533 0
Fax: +49 3641 3533 21
e-mail: cosmoderm2010@conventus.de
Website: www.cosmoderm2010.de

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