ISSN: 1474-015X

Volume 2 Number 1
Spring 2009

Clinical Photodynamics

In Dermatology

An International Newsletter for PDT and FD in Clinical Practice

Editorial

In this issue, we remember the great contribution to research in skin cancer PDT made by Allan Oseroff, from Roswell Park Cancer Institute in Buffalo, who died in October, after his own long battle with cancer. He was fascinated by the mechanism of PDT and his enquiring mind promoted the translation of PDT into the clinic. Let us strive to continue to explore the potential of this therapy!

The annual meeting of Euro-PDT, taking place in Noordwijk, the Netherlands on 13-14th March, will certainly explore the spectrum of applications of PDT in skin disease and encourage its wider use in the clinic. A meeting report will follow in the next issue of ***Clinical Photodynamics***.

We include a meeting report from the UK PDT Skin Group, who held a training day recently, attracting many local dermatologists and covering the science as well as the clinical delivery of PDT. Initially, PDT was provided by only a few enthusiasts in the UK. Now over 150 centres provide the treatment, with acceptance of the contribution that PDT can make to clearing various skin cancers. A future issue of ***Clinical Photodynamics*** later this year will look towards making more use of PDT in immunocompromised patients and at its potential use in seeking to prevent skin cancer.

PDT as a practical and effective modality in photorejuvenation, inflammatory and infectious dermatoses is yet to be established, but the wealth of publications and meeting presentations suggest we should persevere in optimising protocols for the most promising indications.

Colin Morton
Stirling, Scotland

UK PDT Meeting

13th November, 2008
The Wellcome Trust
183 Euston Road, London

Sponsored by Galderma UK

Chairman: Dr Steve Keohane
(St Mary's Hospital, Portsmouth)

Prof Alex Anstey
Dr John Ashworth
Dr Sandra Campbell
Dr Alison Curnow
Dr Tony Downs
Dr Russell Emerson
Dr John Lear
Dr Colin Morton
Ms Paula Oliver
Dr Dafydd Roberts

Figure 1:
Map of PDT Centres in the UK.

DELEGATES to this inaugural UK PDT Meeting were welcomed by the Chairman, Dr Steve Keohane. He noted that the use of PDT had increased dramatically over the past decade and was now available in nearly 150 private and NHS centres across the UK (Figure 1). The agenda for the day explored a broad range of topics, from basic science to practical advice for establishing a clinical PDT practice.

In this Issue

BASIC PRINCIPLES OF PDT

Dr Alison Curnow gave a brief overview of how PDT is currently believed to work. She emphasised that PDT is a non-thermal technique that requires sufficient amounts of three key elements to be present simultaneously: a photosensitiser drug; light of the correct wavelength to excite that drug; and molecular oxygen[1]. The photosensitiser needs to be pre-administered to allow sufficient build-up in the target tissue, prior to activation by exposure to light of the specific wavelength, in the presence of molecular oxygen, to form a cascade of highly reactive oxygen species (ROS) that produce localised tissue damage. ROS have to be present in sufficient quantities to cause target cell death by necrosis/apoptosis.

Photosensitisers

There are a number of photosensitisers, some of which are applicable for use in dermatology. Aminolevulinic acid (ALA) is a pro-drug in the haem biosynthesis pathway, which is up-regulated in tumour cells, thus neatly allowing a selective build-up in the target tissue. ALA is metabolised to protoporphyrin IX (PPIX), a natural photosensitiser that is activated by light at 635nm. This creates singlet state PPIX, which produces the fluorescence that is highly useful in photodiagnosis, but a lesser amount of triplet state PPIX molecules are also created and from these, in the presence of oxygen, a cascade of ROS is produced, resulting in cellular damage.

The efficiency of ALA-PDT has been enhanced by the development of a synthetic version, known as methyl aminolevulinate (MAL: Metvix®). MAL is more lipophilic than ALA, with enhanced cellular uptake and quicker and increased production of PPIX. In turn, this allows a shorter drug-light interval and a lower light dose to be used[2].

Light Sources

Due to the nature of dermatological PDT, where large areas of skin need to be treated, non-laser light sources are generally more practical and are also cheaper and easier to use than lasers. The development of filtered arc-lamps and light-emitting diodes (LEDs) has enabled greater efficiency of light delivery at the correct wavelength, which in turn allows use of lower energy doses, measured in J/cm^2.

Non-invasive fluorescence imaging is a useful way of assessing the amount of PPIX in the treatment area. Following prodrug application, PPIX accumulation can be monitored as fluorescence levels increase and, after effective irradiation, photobleaching can be observed as fluorescence levels are dramatically reduced (**Figure 2**).

Oxygen

The third, and least understood, component of PDT is oxygen. It is important that the PDT treatment doesn't outstrip the local oxygen supply, so the fluence rate (measured in mW/cm^2) needs to be kept relatively low. Experimental data indicate that giving the light dose in fractions[3], with a period between to allow re-oxygenation of the tissue before the next fraction is given[4], may offer a greater overall PDT effect, but the clinical use of this technique is still to be ascertained.

EVIDENCE FOR PDT/GUIDELINES

Dr Colin Morton examined the considerable body of published evidence for the efficacy of PDT in non-melanoma skin cancer (NMSC). In particular, he focused on comparative clinical trials against existing treatments such as cryotherapy, 5-fluorouracil and imiquimod, in which PDT has shown similar outcomes to the standard therapy. He observed that clinically significant skin lesions often have sub-clinical lesions in the same area, which is known as field cancerisation: PDT offers the chance to treat these sub-clinical lesions simultaneously. Furthermore, PDT offers a cosmetic advantage, since healing occurs without scarring, and patient compliance is good, as control remains with the clinician, instead of requiring patients to apply treatments at home.

NMSC lesions that are most likely to benefit from PDT include actinic keratoses (AKs) of thin and moderate thickness on the face and scalp[5], although AKs on acral sites can still be usefully treated with PDT. In Bowen's disease, there is good evidence to use PDT as first-line therapy[6], especially in relatively poor healing sites such as the lower leg. In superficial basal cell carcinoma (sBCC), PDT offers a better cosmetic outcome than surgery[7], although the recurrence rates after PDT are higher (approx. 10%). A similar situation applies in thin nodular BCC (nBCC) but, intriguingly, some 5-year follow-up data[8] have indicated that, after 3 years, no new recurrences are seen. Thus, in BCC cases with a low risk of recurrence, PDT can offer a useful alternative to surgery.

PDT also offers an alternative for patients who are poor candidates for surgery: the elderly, diabetics and patients who are prone to multiple NMSC over time, such as organ transplant recipients. Dr Morton closed by re-emphasising the cosmetic benefits of PDT, since an important goal of any treatment should be patient satisfaction with the outcome.

Guidelines for PDT

The introduction of Metvix® and a body of new evidence that shows the long-term efficacy of PDT has highlighted the need for updating and publication of new guidelines for the use of PDT in dermatology. Therefore, the International Society for PDT (I-PDT) undertook a wholescale re-evaluation of the available literature and produced a set of guidelines that were published in 2007 in the *Journal of the American Academy of Dermatology*[9]. Further in-depth reviews have been published on behalf of the British Association of Dermatologists as more trials have reported their results, the most recent at the end of 2008[10].

PDT: THE PRACTICAL PROCEDURE

Ms Paula Oliver described the role of the PDT specialist nurse, with particular

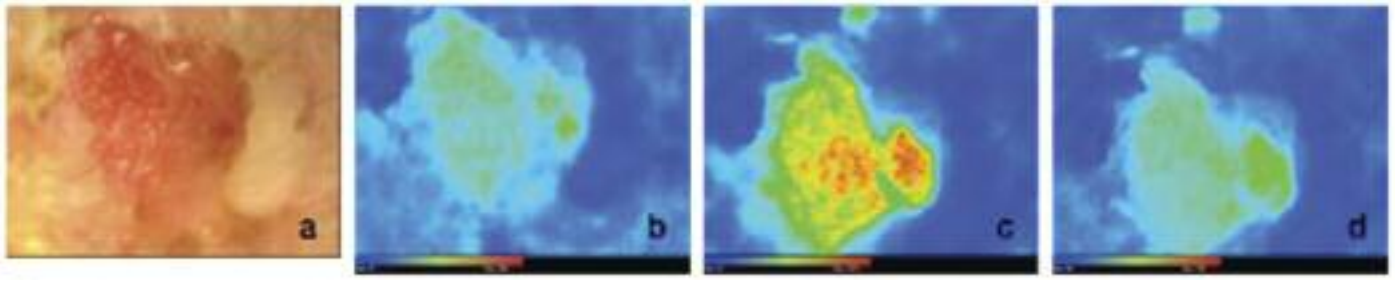


Figure 2: Non-invasive imaging of actinic keratosis during PDT: a) white light image, b) corresponding fluorescence image (before PDT), demonstrating the natural autofluorescence of the lesion, c) fluorescence image following 3 hours of Metvix® application, indicating substantial PPIX accumulation had occurred and d) fluorescence image taken immediately after 37J/cm^2, 635nm irradiation, demonstrating that substantial photobleaching occurred during the light exposure.

emphasis on pre-treatment discussions with the patient, preparation of the site, management of side-effects (especially discomfort during illumination) and follow-up.

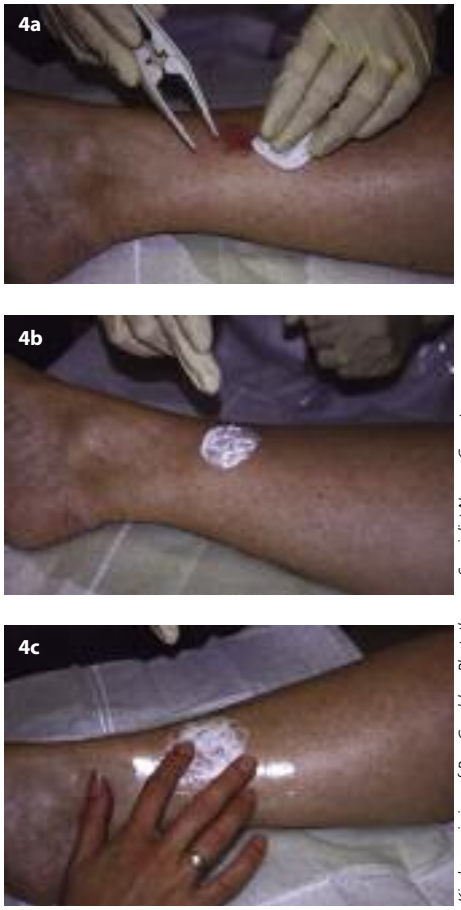
The duration of skin exposure to the chosen photosensitiser, prior to illumination, varies: non-formulary solutions of ALA are usually applied for 4-6 hours, which is considered to be sufficient, although the US FDA licence requires a 14-18 hour application time. However, a number of US practitioners now use even shorter application times of 0.5–3 hours. Metvix® (MAL)-PDT is licensed for a 3-hour application prior to illumination. Both photosensitisers require the treatment area to be covered with an occlusive dressing during the application time. Over the years, a wide variety of light sources have been used with topical PDT, with the general trend being towards more efficient and easier to use devices.

The pre-treatment discussion (**Figure 3**) is an important stage in the PDT process and should be approached as more than a simple collection of a patient's past history and medical records. She noted that patients can be in awe of the physician or have only a loose recollection of what was said to them and therefore prefer to raise questions with the nurse about their ailment and what the treatment will involve.

- Past history, medication, allergies
- Patient's understanding of diagnosis and the proposed PDT treatment
- Preparation of lesion
- Side-effect management (especially pain/discomfort and options available to alleviate them)
- Post-treatment care of treated area
- Follow-up arrangements

Figure 3: Nurse consultation with the patient.

Another major factor in treatment success is the preparation of the lesion, which includes debridement of the treatment area, by ring curette, scalpel or forceps, as the individual nurse prefers (**Figure 4a**). If the area is particularly hyperkeratotic, then a prior softening treatment, such as salicylic acid, vaseline or a hydrocolloid dressing, can be very useful. A skin marker pen can be used to indicate the total area to be treated (usually 0.5-1.0cm from the border of the lesion). The photosensitiser (in this case, Metvix® MAL cream formulation) is applied in a 1mm thick layer over the lesion and surrounding area with a gloved finger or spatula (**Figure 4b**) and then covered tightly with tegaderm or similar, followed by an occlusive dressing (**Figure 4c**) and left for 3 hours to allow accumulation of PPIX in the target tissue.



Kind permission of Bev Gambles, Phototherapy Specialist Nurse, Gwent

Figure 4: Lesion preparation.
a) Debridement of the lesion.
b) Application of MAL cream.
c) Sealing of the treatment area and application of occlusive dressing.

The dressing is then removed and excess cream wiped away. The area can be examined for fluorescence in the target tissue with the use of a Woods lamp. The patient should wear dark goggles during the procedure, whereas the operator can wear blue goggles, which will remove the 'dazzle' of the red light and allow them to see what they are doing. For MAL-PDT with an Aktilite LED lamp, a dose of 37J/cm^2 is given for 8-10 minutes, with the lamp positioned 5-8cm away from the lesion being treated. Two light sources can be used for larger lesions, or for treating two different areas simultaneously (**Figure 5**).

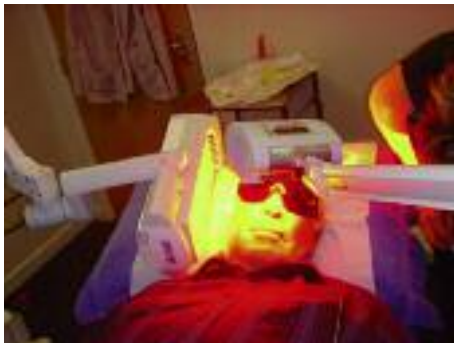


Figure 5: Illumination.

After treatment, the area can be checked for photobleaching with a Woods lamp, then given a suitable dressing for the next 24-48 hours. It is useful to remind patients verbally and in writing that the lesion will look worse for a week or two, before the healing process begins to take place. Follow-up will be as per protocol, usually with the first visit taking place 3 months after treatment.

DEPARTMENT OF HEALTH AND PDT

Dr Dafydd Roberts discussed the implications of recent UK government reports and National Institute for Clinical Excellence (NICE) guidance that affect British dermatologists. NICE guidance recommends that UK cancer networks should establish two levels of dermatological multidisciplinary teams (MDTs), these being at local hospital level and at cancer centres. Any clinician who treats skin cancers should be a member of an MDT.

Patients with precancerous lesions (AKs, Bowen's disease) may be treated by a general practitioner (GP). Alternatively, the GP may refer them to another GP with a specialist interest in dermatology (GPSI) or to a hospital specialist. If there is doubt about the diagnosis, the patient should be referred to a hospital specialist, but follow-up may be with the GP. Patients with low-risk BCC may be diagnosed, treated and followed up by a member of an MDT or a hospital specialist. High-risk BCCs, squamous cell carcinomas (SCCs) and malignant melanomas (MMs) should always be referred to a hospital specialist. Dermatologists should see all suspicious pigmented lesions and should deal with most BCCs, SCCs and melanomas. GPs should not biopsy any potential MMs or treat any skin cancers, although GPSIs may treat low-risk BCCs.

Under the NICE Improving Outcomes Guidance (IOG), PDT is specifically mentioned as an optional treatment for AKs, Bowen's disease and BCCs which should be available for use by clinicians. Therefore, any UK dermatology department which does not have access to PDT can use the IOG to support an application to develop a PDT service. The 2006 NICE Interventional Procedure Guidance for PDT also states that the evidence for its use in AKs, Bowen's disease and BCC is 'adequate', with no major safety concerns, but in SCC the recurrence rates are high, with risk of metastases.

The Department of Health's (DoH) Cancer Reform Strategy states that, by 2012, Britain's cancer services 'can and should become among the best in the world'. The document also highlights PDT as a therapy that should be more widely used by 2012. Additionally, the All-Party Parliamentary

Group's (APPG) 2008 Report on Skin Cancer recommends that all patients must be able to access PDT if it is clinically appropriate. Therefore, Dr Roberts concluded that PDT is recognised as being an appropriate treatment, endorsed by the UK DoH, NICE and APPG reports and should be available for all patients, regardless of location.

PDT IN DIFFICULT-TO-TREAT PATIENTS

Dr Steve Keohane presented data on PDT in organ transplant recipients (OTRs) and patients with vulval intraepithelial neoplasia (VIN). OTRs are at high risk of developing certain cancers, particularly the viral-associated cancers such as skin cancers, due to the profound immunosuppression given to prevent rejection of the transplanted organs (**Figure 6**). Some older immunosuppressive drugs have even been shown to have carcinogenic activity: however, the exception is sirolimus, a new immunosuppressant that also has an antiproliferative action and may have great potential in future cancer treatments.

- 5.2% of transplant patients die because of skin malignancies; 63% result from SCC*
- Numbers and aggressiveness of tumours are also increased:
  - SCC increased 40–250 fold
  - BCC increased 10-50 fold
  - MM increased 10 fold
- Need for treatment and prevention of NMSC on large skin areas, due to field cancerisation

*Cincinnati Tumor Registry

Figure 6: Skin cancers in organ transplant recipients.

Prevention of development of SCCs in OTRs is clearly of interest: with its ability to deliver field treatment, PDT is an attractive option for prophylaxis. A multicentre, randomised trial[11] of Metvix® (MAL)-PDT in OTRs with NMSC has demonstrated that less new AKs appear in areas treated with MAL-PDT than in control areas. Interestingly, patients who received their transplant less than 15 years before entering the trial showed a greater reduction in new AKs than those who were more than 15 years out from transplantation. Larger comparative trials are required to confirm these results.

VIN is another viral-associated disease that is increasing in frequency, has the potential to progress to malignancy and is difficult to treat conventionally. A Phase II study[12] that combined two courses of PDT with initial imiquimod treatment has shown promising results, with 65% of the women being symptom-free at 1 year after treatment, compared to 5% at baseline.

EXTENDING APPLICATIONS FOR PDT

Dr Sandra Campbell examined the possibilities for enhancing the impact of PDT in thicker lesions that currently respond less favourably to the modality. Fluorescence microscopy has shown that insufficient PPIX is present in the deeper areas of nodular BCCs to allow PDT to work[13]. In theory, if the natural pathway of PPIX conversion to haem could be blocked, then more PPIX would build up in the deeper tissues. An iron chelator could block this conversion, and initial studies with a small novel iron chelating agent, CP94, which can be added to the MAL cream formulation, have been promising, even leading to complete clearance of non-debrided nodular BCCs[14, 15].

Dr Campbell also presented a number of case studies showing success with PDT for new indications, including penile intraepithelial neoplasia (PIN), VIN[16], extra-mammary Paget's disease, granuloma annulare and sarcoidosis. Some patients with conditions such as acne, ulcers or extensive scarring may also benefit from PDT. A list of conditions currently being investigated for treatment with PDT is shown in **Figure 7**.

- Alopecia areata
- CDNHC
- Darier's Disease
- Gorlin's Syndrome
- Hailey-Hailey Disease
- Hidradenitis Suppuritiva
- Hirsutism
- Leg Ulcers
- Lichen Planus
- Lichen Sclerosus
- Acne
- Granuloma Annulare
- PIN / VIN
- Molluscum Contagiosum
- Naevus Sebaceous
- Actinic Porokeratosis
- Port Wine Stain
- Acne Rosacea
- Sarcoidosis
- Scleroderma
- Sebaceous Gland Hyperplasia
- Mycosis Fungoides
- Cutaneous Infections
- X-ray Dermatitis
- Scarring
- Skin Rejuvenation

S.Campbell 2008

Figure 7: New indications for PDT.

QUESTION AND ANSWER PANEL

Delegate: How about PDT in keloid scars?

Dr Campbell: I give 2 treatments with triamcinolone, 3-6 weeks apart, then treat with 2 sessions of PDT 2 weeks later.

Delegate: How much debulking should be done for nodular BCCs?

Dr Morton: There is much debate about this, and great differences in practice between the published studies. I think that the amount of debulking needs to be enough to effectively convert a 'thick' lesion into a 'thin' lesion, but heavy curettage can have its own problems with excessive bleeding, etc: careful patient selection is the key.

Delegate: What is the ideal time period between curettage and performing PDT?

Dr Morton: There may be some advantage to performing debulking 2-3 weeks before PDT, but there's very little data on this: a proper trial is needed. However, I also want to emphasise that, at present, PDT for thick nodular BCC isn't recommended unless conventional treatment options are not suitable.

Delegate: Have enhancement creams been used, to try to increase the depth of PDT action?

Dr Curnow: Yes, but with little actual benefit.

Delegate: Has PDT been used in Kaposi's sarcoma?

Dr Keohane: Dr Hopper's group at UCL have examined this: whilst it may not be curative, PDT does have a beneficial palliative effect.

Delegate: Local anaesthetics can reduce the side-effect of pain, but they also cause vasoconstriction: as PDT requires oxygen to work, does this limit the amount of available oxygen?

Dr Campbell: Yes, it would, so an anaesthetic that doesn't have a vasoconstrictive effect, such as lignocaine, may be a better alternative. Additionally, anything that affects local blood supply, such as laser cooling devices, should be carefully considered before use. However, we don't find that local anaesthesia is necessary.

Delegate: Conversely, then, can hyperbaric oxygen increase the PDT effect?

Dr Curnow: There is some evidence that hyperbaric oxygen does increase the PDT effect, but the benefit doesn't justify the extra equipment and effort that is necessary. We prefer to concentrate on pharmacological routes to improve PDT. In any case, because we are treating dermatological lesions, much of the oxygen required for PDT is available from the atmosphere.

Delegate: Would an ultrasound scan be able to provide a quick measurement of the depth of a nodular BCC and therefore give an easy assessment of whether that lesion is likely to respond to PDT or not? Secondly, could the photosensitiser be injected directly into a nodular BCC?

Dr Campbell: I was discussing the option of direct injection with a member of this audience earlier today: the trial she was involved with was abandoned as they were getting too many foreign body reactions.

Dr Ashworth: From what has been presented today, it's clear that PDT is advancing at a rapid pace. Moreover, there may be some useful insights, positive and negative, to be gained from individual practice across the country, which is the type of information that never finds its way into formal publication. It would

be very useful if there was some kind of PDT Forum available for clinicians and scientists to share their experiences of PDT.

Delegate: Is this something that Galderma would be prepared to host on the company website?

Ms Jemma Cooke: Yes, we could investigate this.

BREAKOUT SESSION: FINANCIAL AND COMMISSIONING CONSIDERATIONS

1. Setting up PDT in the NHS

Dr Tony Downs began by emphasising the aspects of PDT that make it a justifiable service to offer within the NHS structure. PDT is recommended by NICE as part of a comprehensive skin cancer service, is increasingly requested by patients, can be nurse-led, has excellent cosmesis and is an option for patients who are poor candidates for surgery. Assuming that a weekly PDT clinic would treat 5 patients on that day, with 40 treatment weeks available per year, then 200 patients can be treated per year. Dr Downs' own calculated average costs per patient are £122.00, with the breakdown shown in **Figure 8**.

		£
Nurse Specialist		14.00
Consumables		1.00
Metvix® Cream:-	BCC:	128.00
	Bowen's disease:	163.00
	AK (SCC in situ):	65.00
Room Availability		??
Aktilite Light Source		5000.00 (but cost is deferred with bulk purchases of Metvix®)

Figure 8: Costs to the NHS per patient.

There are 2 Healthcare Resource Group (HRG) codes for PDT: J34 covers a day case in a 'frail' patient and is £1269.00, whereas J35 covers a day case in a fit patient and is £764.00. Therefore, taking the NRG J35 code as the standard, the annual tariff for 200 patients would be £152,800, minus the cost of treatment (£122.00 x 200 = £24,400), providing an attractive annual income of £128,400. Alternatively, if a non-day case route is required (with gross income of £60 per patient), then the cost of Metvix could be deferred back to the Primary Care Trust (PCT) by having it prescribed as an FP10. Removing the drug cost from the cost per patient would generate an income over cost of approximately £40 per patient. However, clinicians may also be able to negotiate fees on a per patient basis with local PCTs.

There are also hidden benefits of PDT. It is comparatively cheaper than complex surgical intervention, with virtually no post-procedural wound complications, and fewer hospital visits for patients.

2. PDT in the Private Sector

An example of private practice costs for PDT was described by Dr Russell Emerson (**Figure 9**). He noted that the clinic fees are negotiated individually with insurance companies and so are variable.

3. Running a Successful Practice Incorporating PDT

Dr John Ashworth shared his personal experience of PDT and the practical lessons

PRIVATE FEES

Initial Assessment:

New Patient Consultation	£ 180.00
Skin Biopsy S1500	£ 91.00
Local Anaesthetic AC100	£ 22.25
	£ 293.25

Follow-Up Review:

Follow-Up Consultation:	£ 130.00

Photodynamic Therapy Treatment:

Photodynamic Therapy S0606 Session 1	£ 300.00
+/- Local Anaesthetic AC100	£ 75.00
Photodynamic Therapy S0606 Session 2	£ 300.00
+/- Local Anaesthetic AC100	£ 75.00
	£ 750.00

Follow-Up Reviews:

3-Month and 9-12 month Follow-up Visits	£ 260.00

Total Income = £1433.25

CLINIC FEES (Negotiated Individually)

Treatment Room Fees/Skin Biopsy:

Package Price Including Histology	£ 335.00

Photodynamic Therapy Treatment:

Photodynamic Therapy S0606 Session 1	£ 593.00
Photodynamic Therapy S0606 Session 2	£ 593.00

PDT Session Price
£593-£724 Per Session
Including Cream

Total = £ 1521.00

Figure 9: Insured private consultant and clinic/hospital fees for PDT.

to be learned. Firstly, any PDT service is essentially a business which aims to make a profit and must be approached in that vein, with a plan that examines the ideal type and numbers of patients to be treated, the likely take-up in the area, size of practice to be established, local competitors, site (within a hospital or a separate building), capital costs, staff recruitment, and who will pay for it all: the NHS, the private sector, or a proportion of both. Secondly, it is important to recognise that it will require large amounts of personal time and effort to establish and run. Thirdly, PDT will probably be one of several modalities being offered which, combined with the persona of the clinician, will influence the style of practice: either primarily a skin cancer clinic or a cosmetic dermatology service. Equally important is the careful recruitment of any other therapists, nurses and secretarial staff, whose personalities need to be in tune with the business plan just as much as their qualifications and experience. Private patients will expect more of their PDT experience, which applies both to the comfort of their surroundings and the degree of service they receive from all staff.

If the practice is part-time within a larger organisation, consideration needs to be given to where light sources and stocks are stored when not in use. Some equipment (e.g. intense pulsed light [IPL] devices) may have other applications outside PDT, in which case costs may be shared with colleagues or used to broaden the base of patients being treated.

PHOTOREJUVENATION

Dr John Ashworth and Dr Tony Downs discussed their experience of using Metvix® (MAL)-PDT with the Aktilite and IPL in a series of patients to achieve photorejuvenation. International interest in this concept has been growing, as photorejuvenative effects have often been observed in the skin surrounding PDT-treated lesions, with reduction of wrinkles and solar lentigo. PDT is also less potentially harmful than alternatives such as chemical peels and laser resurfacing. As this is a purely cosmetic treatment, prior patient education about possible pain and the inflammation that will follow a PDT session is particularly important. The inflammation appears to be necessary in order to achieve the best results, but can be alleviated with ice packs.

Not all IPL devices are ideal for use in PDT: Dr Downs recommended a 'square pulse' device, set to deliver a triple pulse to allow tissue reoxygenation, with multiple passes over the treatment area, according to the degree of skin imperfections being treated. The process is quick, allowing large skin areas to be treated and, significantly, patients do not seem to suffer pain during IPL irradiation.

MANAGING PDT COMPLICATIONS

Dr Steve Keohane focused on the management of erythema and pain in PDT. Erythema is a result of the phototoxic reaction, but MAL-PDT results in significantly less erythema than ALA-PDT. Similarly, MAL-PDT appears to cause less peri- and post-treatment pain than ALA-PDT. These differences are primarily due to the greater selectivity of Metvix® uptake into the lesional tissue versus normal tissue, but also ALA is taken up by gamma-receptors on the peripheral nerves. Many of the ways of managing patient pain/discomfort during treatment had already been alluded to by previous speakers (**Figure 10**).

In some cases, pain can be predicted: certain sites (e.g. temples, forehead) are apparently more painful to treat, and male sex is a strong predictor of pain! There are higher reports of pain being experienced during second and subsequent PDT sessions, compared to the first session. Intriguingly, in a trial that compared solar (daylight) illumination to standard LED illumination to activate PPIX, significantly less pain was reported by the patients who underwent daylight illumination. The use of transcutaneous electrical nerve stimulation (TENS) may have a role in patients who have suffered severe pain in prior PDT sessions, and Dr Keohane has found that nerve blocks are effective in cases of extensive disease.

- Pre-, peri- and post-treatment explanation, including patient information leaflets/videos
- Pre-treatment painkillers (e.g. paracetamol)
- Distraction:
  - Music/stress ball/communication with operator
  - 'Talk anaesthesia', especially by nurse
  - Aromatherapy/other complementary therapies
- Cooling techniques:
  - Water spray/fans/laser cooling devices
  - Ice packs after therapy
- Local anaesthetic
- Entonox in some centres

Figure 10: Management of PDT/discomfort pain.

References

1. Henderson B and Dougherty T 1992 *Photochem Photobiol* **55** 145-157
2. Peng Q *et al* 1997 *Cancer* **79** 2282-2308
3. Curnow A *et al* 2006 *Lasers Surg Med* **38** 325-331
4. Curnow A *et al* 2000 *J Photochem Photobiol B: Biology* **58** 149-155
5. Morton C *et al* 2006 *Brit J Dermatol* **155** 1029-1036
6. Morton C *et al* 2006 *Arch Dermatol* **142** 729-735
7. Szeimies R-M *et al* 2008 *JEADV* **22** 1302-1311
8. Rhodes L *et al* 2007 *Arch Dermatol* **143** 1131-1134
9. Braathen L *et al* 2007 *JAAD* **56** 125-143
10. Morton C *et al* 2008 *Brit J Dermatol* **159** 1245-1266
11. Wennberg AM *et al* 2008 *Transplantation* **86** 423-429
12. Winters U *et al* 2008 *Clin Cancer Res* **14** 5292-5299
13. Campbell S *et al* 2007 *J Environmental Pathol Toxicol Oncol* **26** 295-303
14. Campbell S *et al* 2008 *Brit J Dermatol* **159** 387-393
15. Pye A *et al* 2008 *J Cancer Res Clin Oncol* **134** 841-849
16. Campbell S and Curnow A 2008 *J Eur Acad Dermatol Venereol* **22** 502-503

Useful Websites

European Society for PDT:
www.euro-pdt.org
Peninsula Medical School:
www.pms.ac/pms/research/dermatco.php

Professor Allan Oseroff (26/06/43-16/10/08) – An Appreciation

Allan R. Oseroff, PhD, MD, was Professor and Chair of the Department of Dermatology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo. He held joint appointments in Molecular & Cellular Biophysics, Pharmacology & Therapeutics, and the Lawrence P. and Joan Castellani Chair in Dermatology, Roswell Park Cancer Institute.

He was born in Jersey City, New Jersey, and graduated from Princeton University. He earned his doctoral degree in Applied Physics from Harvard University, Cambridge, Massachusetts, in 1971, and his medical degree at Yale University Medical School, New Haven, Connecticut, in 1977. He completed residency training in Medicine and Dermatology at the University of Chicago in 1980, and fellowship training at Stanford Medical Center, Palo Alto, California, in 1982. Allan joined the staff of Roswell Park Cancer Institute in 1990.

His research interests focused on photomedicine; mechanisms of photodynamic therapy; new photosensitisers; molecular responses; effects of PDT on T-lymphocytes and antigen-presenting cells; electroporation; and imaging. I had the opportunity to work with Allan at Roswell Park briefly in 1995. He had a passion for PDT that was obvious to all who met him. Allan authored or co-authored more than 200 journal publications, book chapters and abstracts. He was a member of the Editorial Board of *Lasers in Surgery and Medicine*, and was a referee for many journals, including *Nature*, *Science*, and the *Journal of the National Cancer Institute*. Despite his multiple roles, I always found him pleasant and considerate, ready to ask the hard questions about mechanisms and the rationale for observed results!

Colin Morton
Stirling, Scotland

Recent papers include:

Irradiance-dependent photobleaching and pain in 5-aminolevulinic acid photodynamic therapy of superficial basal cell carcinomas. Cottrell WJ *et al* 2008 *Clinical Cancer Research* **14** 4475-4483

Photodynamic therapy for non-melanoma skin cancer. Fien SM, Oseroff AR 2007 *Journal of the National Comprehensive Cancer Network (JNCCN)* **5** 531-540

PDT as a cytotoxic agent and biological response modifier: Implications for cancer prevention and treatment in immunosuppressed and immunocompetent patients. Oseroff AR 2006 *J Investigative Dermatol* **126** 542-544

Treatment of diffuse basal cell carcinomas and basaloid follicular hamartomas in nevoid basal cell carcinoma syndrome by wide-area 5-aminolevulinic acid photodynamic therapy. Oseroff AR 2005 *Arch Dermatol* **141** 60-67

Prime Time PDT

An international roundup of PDT-related papers and publications

Guidelines for Topical Photodynamic Therapy: Update

Morton C, McKenna K, Rhodes L 2008 *Brit J Dermatol* **159** 1245-1266

On behalf of the British Association of Dermatologists (BAD), the authors have produced an update of the 2000 workshop and report by the British Photodermatology Group. A number of multicentre randomised controlled studies have demonstrated high efficacy of topical PDT for actinic keratoses, Bowen's disease (BD) and superficial basal cell carcinoma (BCC), and also efficacy in thin nodular BCC. Long-term follow-up studies have also been published, indicating that the recurrence rates are comparable to other standard therapies in BD and superficial BCC. In nodular BCC, sustained efficacy is still lower than surgery. Additionally, these long-term studies provide reassurance over the safety of repeated use of PDT. Current evidence does not support the use of topical PDT in squamous cell carcinoma. PDT can reduce the number of new lesions in patients with a high risk of developing skin cancer and may also offer a preventive therapy. There is insufficient evidence for PDT in treating psoriasis, but it may have potential in other inflammatory/infective dermatoses, and the evidence base is growing for its use in acne and also in aspects of photoageing. Pain is an issue in a minority of patients, but otherwise PDT is well tolerated.

Nerve Blocks Enable Adequate Pain Relief During Topical Photodynamic Therapy of Field Cancerization on the Forehead and Scalp

Halldin CB, Paoli J, Sandberg C *et al* 2009 *Brit J Dermatol* Jan 28 (E-Pub ahead of print)

In this study, nerve blocks were demonstrated to be significantly effective in pain relief during PDT involving the forehead and scalp ($P < 0.0001$). Ten men with extensive and evenly distributed actinic keratoses (AKs) of the forehead and scalp were given nerve blocks to one side prior to PDT, whilst the other side served as a control. The mean visual analogue scale (VAS) score on the side given anaesthesia was 1, which compared to 6.4 on the unanaesthetised side. The authors concluded that nerve blocks can be used for anaesthesia during PDT, but that pain relief should be tailored to the needs of each individual patient.

Influence of Formulation Factors on PpIX Production and Photodynamic Action of Novel ALA-Loaded Microparticles

Donnelly RF, McCarron PA, Al-Kassas R *et al* 2009 *Biopharm Drug Dispos* **30** 55-70

A new 5-ALA-containing microparticulate system has been developed, which maintains the stability of ALA during storage, but then releases the drug at skin temperature. The authors tested the production of PpIX when the microparticles were formulated in different vehicles and applied to the skins of animals. Propylene glycol gel vehicles were found to result in the highest PpIX fluorescence in normal mouse skin. When WiDr tumours were implanted subcutaneously, they continued to grow in untreated controls, but growth was inhibited when treated with either the ALA microparticles alone or the microparticles in propylene gel, followed by a single laser irradiation. The gel formulation was shown to reduce tumour growth rate by 105%, compared to 89% with the microparticles alone. Following these promising results, the authors aim to use ALA-microparticle-loaded gels in a future exploratory clinical trial.

Pilot Study on Photodynamic Therapy for Acne using Indocyanine Green and Diode Laser

Kim BJ, Lee HG, Woo SM *et al* 2009 *J Dermatol* **36** 17-21

A group of 16 randomly chosen Korean patients with acne vulgaris were treated by PDT using indocyanine green (ICG) and a diode laser. The group was divided into two sub-groups to receive either a single treatment or multiple treatments (3 treatments with a 1-week interval between each treatment). The patients were followed up after 2 months and assessed. Although PDT was effective in treating their acne, multiple treatments did not yield a better cosmetic result.

Photodynamic Treatment for Viral Infections of the Skin

Rossi R, Bruscino N, Ricceri F *et al* 2009 *G Ital Dermatol Venereol* **144** 79-83

PDT with either ALA or methylaminolevulinate (MAL) has shown activity in a number of new areas against bacteria, fungi and viruses. The authors reviewed these new indications, which include HPV-related skin infections such as verrucae, condylomata acuminata, periungueal warts and epidermodysplasia verruciformis, and also non-HPV-related indications, such as molluscum contagiosum and Herpes Simplex.

Porphyrin Distribution after Topical Aminolevulinic Acid in a Novel Porcine Model of Sebaceous Skin

Sakamoto FH, Tannous Z, Doukas AG *et al* 2009 *Lasers Surg Med* **41** 154-160

Anterior pig ear skin was used as a new model in this study, as it is microanatomically similar to human sebaceous skin. ALA was applied and the accumulation of porphyrins assessed by fluorescence microscopy of biopsies over a 3-hour period. It was observed that there was a variable time-dependent accumulation and strength of fluorescence in different glands. Sebaceous glands started fluorescing at 45-75 minutes after application, whereas eccrine gland fluorescence could be detected at 30 minutes. Hair follicles and sebaceous glands expressed stronger fluorescence than eccrine glands and epidermis. The authors conclude that the results indicate that there are other routes of uptake of topical ALA apart from the trans-epidermal route.

Skin Cancer and the Solid Organ Transplant Recipient

Patel MJ, Liégeois NJ 2009 *Curr Treat Options Oncol* Feb 19 (E-pub ahead of print)

This is a review of the literature on treatment of skin cancers in the organ transplant recipient population, the most common late-post-transplant complication seen in this group of patients. Despite its frequency, there are few published prospective or retrospective studies with multivariate analysis: therefore, opinion largely dominates the treatment recommendations. Not surprisingly, the mainstay of current treatment focuses on total removal or mechanical destruction of the tumours, and the treatment modality depends upon the risk and type of tumour. PDT is highlighted as one of the new treatment modalities. The authors also emphasise the importance of patient education on skin cancer prevention in all age groups.

Are you receiving *Clinical Photodynamics*?

If this is not your personal copy of ***Clinical Photodynamics*** and you would like to receive regular copies directly, free of charge, then please either copy and complete this form and post it, in an envelope, to our Editorial Office or fax or e-mail your details to us (see opposite).

Title: . . . . . .
First Name/Initials: . . . . . .
Surname: . . . . . .
Post held: . . . . . .
Workplace: . . . . . .
. . . . . .

Address for mailing: . . . . . .
. . . . . .
. . . . . .
Country: . . . . . .
Postal/Zip Code: . . . . . .
e-mail: . . . . . .

PLEASE RETURN THIS FORM TO: Eurocommunica Limited
Caxton House, 51 Barnham Road, Barnham, West Sussex PO22 0ER, UK
FAX: +44(0)1243 555043 E-MAIL: EUROCOMMUNICA@sky.com

Calendar of Events 2009

March 13-14, Noordwijk, The Netherlands
9th EURO-PDT Annual Congress
Contact: EURO-PDT 2009 Congress Secretariat
Tel: +33 (0)1 46 43 33 42 Fax: +33 (0)1 46 24 88 38
e-mail: europdt2009@vista-fr.com
Website: www.euro-pdt.org

April 23-26, Bucharest, Romania
6th Spring Meeting of the European Academy of Dermatology and Venereology (EADV)
Contact: Symposium Secretariat, Romania Travel Plus,
56 Tudor Stefan St. Sector 1, 011658 Bucharest, Romania
Tel: +40 21 230 42 82 Fax: +40 21 230 50 42
e-mail: info@eadvbucharest2009.com
Website: www.eadv.org/bucharest2009

May 3-6, Tel Aviv, Israel
12th World Congress on Cancer of the Skin (WCCS)
Contact: WCCS Meeting Organiser
Tel: +41 229 080 488 Fax: +41 227 322 850
e-mail: wccs2009@kenes.com

May 12-16, Vienna, Austria
Joint Meeting: 7th World Congress on Melanoma/ 5th Congress of the European Association of Dermato-Oncology
Contact: Annette Gleich
e-mail: Annette.Gleich@worldmelanoma2009.com
Website: www.worldmelanoma2009.com

May 17-20, Queensland, Australia
42nd Annual Meeting of the Australasian College of Dermatologists (ACD)
Contact: ACD Meeting Office
Tel: +61 2 8765 0242 Fax: +61 2 9736 2194
e-mail: admin@dermcoll.asn.au

May 20-24, Prague, Czech Republic
10th International Congress on Dermatology (ICD)
Contact: ICD 2009, Guarant International, Opletalova 22,
110 00 Prague 1, Czech Republic
Tel: +420 284 001 444 Fax: +420 284 001 448
e-mail: icd2009@icd2009.com
Website: www.icd2009.com

June 6-11, Seattle, USA
12th World Congress of the International Photodynamic Association (IPA)
Contact: David Kessel
Tel: +1 313 577 1766 Fax: +1 313 577 6739
e-mail: dhkessel@med.wayne.edu

June 18-23, Düsseldorf, Germany
15th International Congress on Photobiology
Contact: Katharina Beyen/Andrea Hardtke, Institut für Umweltmedizinische Forschung (IUF) an der Heinrich-Heine-Universität Düsseldorf gGmbH, Auf'm Hennekamp 50,
D-40225 Düsseldorf, Germany
Tel: +49 (0)211 3389 216
Website: www.iuf.uni-duesseldorf.de/ICP2009

June 25-28, Munich, Germany
American Academy of Dermatology and European Academy of Dermatology and Venereology 'State of the Art' in Dermatology
Contact: AAD/EADV Meeting Organiser
Tel: +847 240 1485 Fax: +847 330 1135
e-mail: mstein@aad.org

June 27, Destin, USA
Optimizing Management of Non-Melanoma Skin Cancers: Current Data and Future Treatment Options
Contact: Meeting Organiser
Tel: +609 921 6622 Fax: +609 921 6428
e-mail: kwetzel@academycme.org

July 1-5, Vancouver, Canada
Canadian Dermatology Association 84th Meeting
Contact: CDA Meeting Organiser
Tel: +613 738 1748 Fax: +613 738 4695
e-mail: contact.cda@dermatology.ca

September 10-12, Budapest, Hungary
39th Annual Meeting of the European Society for Dermatological Research (ESDR)
Contact: ESDR Secretariat
Tel: +41 22 321 4890 Fax: +41 22 321 4892

October 7-11, Berlin, Germany
18th Congress of the European Academy of Dermatology and Venereology (EADV)
Contact: EADV 2009 Secretariat, MCI-Berlin Office,
Markgrafenstr. 56, D-10117 Berlin, Germany
Tel: +49 (0)30 20 45 90 Fax: +49 (0)30 20 45 950
e-mail: registration@EADVBerlin2009.com
Website: www.EADVBerlin2009.com

Published by Eurocommunica Publications, Caxton House, 51 Barnham Road, Barnham, West Sussex PO22 0ER, United Kingdom
Tel: +44 (0)1243 555041/2 Fax: +44 (0) 1243 555043 e-mail: EUROCOMMUNICA@sky.com