Photodynamic therapy for skin cancers

Photodynamic therapy is a step forward in the treatment of superficial skin cancers, achieving excellent cosmesis with relatively few side effects. With further improvements, it may surpass current therapies as first line treatment for certain skin cancers and dermatoses.

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Photodynamic therapy (PDT) is a relatively new technique for the treatment of cancers accessible to light and is showing great promise, especially in the area of superficial skin cancers. The therapy, which involves the use of a photosensitising agent and illumination from a light source, has been available in the clinical setting since the late 1970s for the treatment of oesophageal, bronchogenic, bladder and cervical cancers, the photosensitiser being introduced orally or intravenously and the laser light being applied to the treatment site via a fibre optic. The development of topical photosensitisers has made PDT a more attractive and convenient therapy for skin cancers and other dermatoses because the photosensitiser is applied specifically to the affected areas, thus sparing other sites from unnecessary photosensitisation.

The main advantage of PDT is the excellent cosmetic result (Figures 1 and 2). There is virtually no scarring and inflammatory changes resolve within a week or two. Hypopigmentation can occur on rare occasions, although less so than with cryotherapy. Freckles are usually not affected by PDT.

Mechanism of action

PDT is a two-step procedure. The photosensitiser or its prodrug is administered to the patient and taken up by the target cells. It is then activated in the presence of oxygen with a specific wavelength of light directed to the target tissue. Because the chemical is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesion, damage to adjacent healthy structures is minimised.

The two commonly used topical chemicals are 5-aminolaevulinic acid (ALA) and its methyl ester methyl aminolevulinate (MAL; Metvix), which has improved uptake, probably due to its lipophilicity. ALA and MAL are not photosensitisers themselves but are taken up by skin cancer cells and converted to the photosensitiser protoporphyrin IX via the

IN SUMMARY

- **Photodynamic therapy (PDT) is most suitable for superficial basal cell carcinomas, Bowen's disease and actinic keratoses.**
- **PDT is not effective in treating melanoma and squamous cell carcinomas.**
- **PDT achieves excellent cosmetic results.**
- **The two main topical photosensitisers used are 5-aminolaevulinic acid and methyl aminolevulinate.**
- **The main side effect of PDT is pain.**
- **Regular skin checks are required after successful tumour clearance with PDT as recurrence is possible.**

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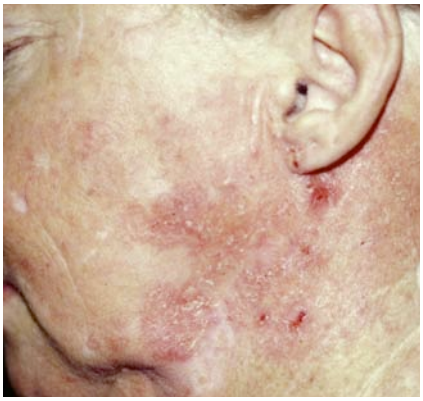
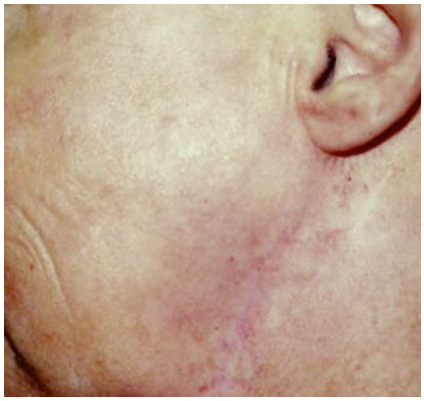
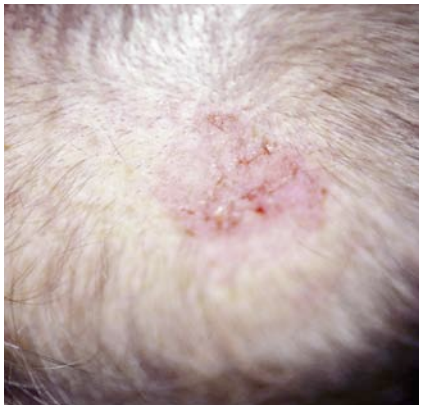
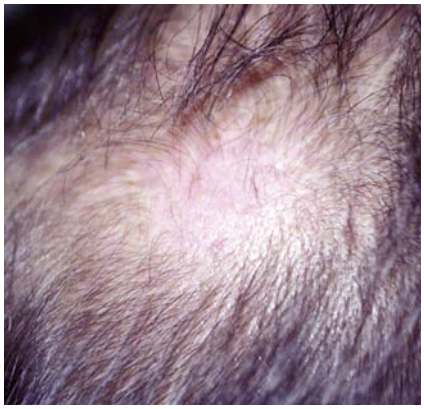




Figures 1a and b. Bowen's disease before (a, left) and three months after (b, right) photodynamic therapy.





Figures 2a and b. Basal cell carcinoma of the scalp before (a, left) and three months after (b, right) photodynamic therapy.

haem pathway. Protoporphyrin IX is activated by the application of visible light in the presence of oxygen, and the reactive oxygen species that are produced cause tumour destruction while surrounding healthy tissues are largely preserved. Red light (about 630 nm wavelength) is recommended because of the depth of penetration that can be achieved. Blue light PDT is available in some centres and is generally used for treating actinic keratoses and acne.

Indications for PDT

PDT can be curative for superficial basal cell carcinomas, Bowen's disease (intraepidermal squamous cell carcinoma, a superficial squamous cell carcinoma *in situ*) and actinic keratoses.

The ideal patients for PDT are those with large superficial basal cell carcinomas, large areas (more than 10 cm^2) of Bowen's disease, or multiple superficial basal cell carcinomas, Bowen's disease and actinic keratoses in the same location. (The lamps used can illuminate areas of up to 8 by 18 cm.) Other treatment modalities, such as surgery or cryotherapy, may be extremely difficult and result in poor cosmesis in patients with large lesions.

Small and/or solitary lesions can also be treated with PDT but, because of the time involved, patients may find other forms of treatment (for example, cryotherapy) more convenient.

PDT has also been used in treating localised cutaneous T-cell lymphoma and in the palliative management of Kaposi's sarcoma. Its role in acne and psoriasis is still experimental. High recurrence rates when used for treating invasive squamous cell carcinoma make it not the treatment of choice for this skin cancer; poor response and high recurrence rates mean it is also unsuitable for cutaneous melanoma.

Before performing PDT, the clinical diagnosis of a lesion should be confirmed and its suitability for treatment determined, particularly the depth of tumour (this may be achieved by performing a 2 to 3 mm punch biopsy). ALA and MAL will achieve concentrations at a depth of 1 to 2 mm that are sufficient to give a therapeutic response.

Differences between MAL and ALA

Before MAL became available, ALA was the only topical photosensitising agent used in Australia. ALA is not approved by the TGA and has to be imported from the USA; MAL was approved in 2003 but is only available directly from the manufacturer, and not by prescription.

The differences between the two agents include:

- the application time for MAL is shorter, about three hours (due to its better uptake), whereas for ALA it is usually about five to six hours
- MAL tends to be more lesion-specific than ALA, with less uptake by surrounding tissue
- MAL is less painful than ALA
- ALA, which is imported as a powder and formulated as an ointment that is unstable, needs to be used within about five days of mixing; MAL is available as a cream and should be used within seven days of the tube being opened.

A 2 g tube of MAL cream (160 mg/g) costs about $450, while ALA as a 20%

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ointment preparation costs about $50 per gram.

Performing PDT

As previously mentioned, PDT is a two-step procedure involving administration of the photosensitiser to the lesion and uptake by the target cells followed by photoactivation in the presence of oxygen. The procedure is described in the box on this page.

Pain and pain relief

Pain is the major side effect of the procedure and results from the marked acute inflammation during and after the process. The intensity of the pain experienced varies widely between patients, and also depends on the type of lesion, the body region being treated, the patient's sex and the size of the lesion (Table 1). The degree of pain does not necessarily correlate with treatment dose, Fitzpatrick skin type, age or fluorescence intensity.

Strategies to reduce pain include cooling the area or infiltrating it with local anaesthetic (Table 2).

It is important to warn patients that they may experience some minimal discomfort after the ointment is applied. Typically, the pain escalates during the light treatment, and it may continue for several hours afterwards. If pain is severe during therapy, irradiation can be stopped and then restarted later.

Patients should also be aware that the inflammation can take seven to 10 days to resolve and that, occasionally, there may be blistering and noninfective pustulation.

Postoperative care

Dressings on treated sites should be replaced daily until the inflammation has settled. Topical vaseline or antibiotics help keep wounds moist and aid re-epithelialisation by preventing infection. Patients should expect a degree of erythema and oedema, sometimes followed by blistering, then crusting and re-epithelialisation. Newly healed skin appears one to two weeks after the treatment, following crusting and peeling of lesions.

Efficacy of PDT

Basal cell carcinoma

Among the basal cell carcinoma subtypes, superficial basal cell carcinoma (less than 2 mm thick) responds best to PDT. Studies comparing PDT using MAL as the photosensitiser (MAL PDT) with cryotherapy for superficial basal cell carcinoma have shown three-month complete

Photodynamic therapy: the procedure

The steps involved in performing PDT in the authors' department are outlined below.

- The treatment site is prepared by gently curetting crusts and scales.
- The ALA ointment or MAL cream is applied in a 1 mm thick layer to the lesion and a 5 mm margin of surrounding tissue.
- A protective dressing is applied to prevent light exposure and the ointment or cream is left in place for about three or five hours for absorption of ALA or MAL, respectively, and its conversion to protoporphyrin IX.
- After the ointment or cream is removed with gauze, areas surrounding the lesion are protected with aluminium foil (Figure A). If MAL is being used, protection with foil is usually not required as this drug is more lesion-specific.
- The patient is positioned so that the site to be treated is at the appropriate distance (about 5 to 8 cm) from the PDT lamp (an Aktilite or Omnilux lamp, which emits red light at about 630 nm; Figure B). Patients are normally treated in the supine or prone position but the sitting position can be particularly useful for lesions on the shoulders.
- Treatment with the lamp is carried out for about 10 minutes (a total light dose of 75 J/cm^2 is required), protective goggles being worn by both the patient and the treating doctor.
- Pain relief is provided as necessary – cool air, local anaesthetic, ice packs or paracetamol or NSAIDs.
- After treatment, a dressing is applied to the treated site, and should be replaced daily until the inflammation settles. The use of topical Vaseline or antibiotic creams helps keep wounds moist and aids re-epithelialisation.

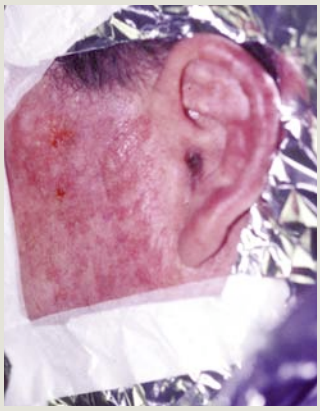

Figure A. The area surrounding a site to be treated with PDT using ALA should be protected with aluminium foil.

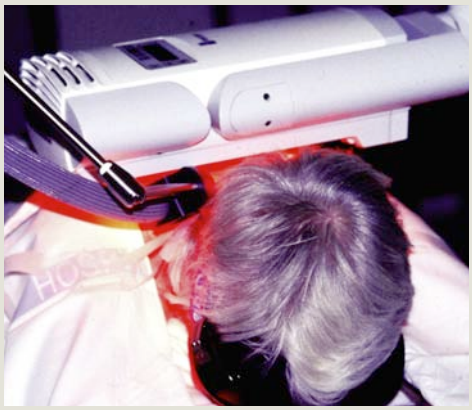

Figure B. A patient undergoing PDT. The Aktilite PDT lamp is positioned about 5 to 8 cm above the site to be treated. Note that the patient is wearing goggles.

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Table 1. Predictors of pain in PDT

- Type of lesion – actinic keratosis more painful than basal cell carcinoma or Bowen's disease
- Region – lesions on head and neck (particularly scalp) more painful than lesions on abdomen or limbs
- Sex – men experience more pain than women
- Size of lesion – larger treated areas more painful than smaller areas

Table 2. Strategies to minimise pain due to PDT

- Cool air from a Zimmer cryo 5 cooler (or a fan)
- Local anaesthetics such as 1% lignocaine (without adrenaline)
- Ice packs
- Paracetamol or NSAIDs (premedicate and/or post-therapy)

response rates of 97% and 95%, respectively, and a superior cosmetic outcome for MAL PDT.

In primary nodular basal cell carcinoma, three-month complete response rates of 91% for MAL PDT and 98% for excision with a 5-mm margin have been shown. For MAL PDT, two lesions recurred within the first 12 months and three in the following 12 months; there were two recurrences at 24 months with surgery. Cosmetic outcome was superior for MAL PDT.

Morpheaform basal cell carcinomas should not be treated with PDT.

Actinic keratosis

Pooled data from several studies comparing MAL PDT with cryotherapy for treatment of actinic keratoses have shown that 77% of lesions responded to a single cycle of PDT, increasing to about 90% with two treatments, whereas 71% of lesions responded to cryotherapy. In addition to better response rates, MAL PDT offered a superior cosmetic outcome than cryotherapy. Actinic keratoses of the head and neck tend to respond better compared to those of the extremities.

Bowen's disease

A randomised placebo-controlled multicentre study comparing MAL PDT with cryotherapy and topical 5-fluorouracil (5-FU) therapy has shown that the patient response rate of 91% with MAL PDT was equivalent to those rates achieved with cryotherapy and 5-FU. Again, MAL PDT had the advantage of a better cosmetic outcome.

Frequency of PDT

Studies in Europe indicate that double treatment with ALA PDT seven days apart is superior to single treatment for basal cell carcinoma. In our department, PDT is normally repeated four weeks later; this is longer than is usual in Europe because the skin cancers in Australia are larger, resulting in more inflammation, which must be allowed to settle before the second treatment. The longer time between treatments may reduce the degree of pain experienced by patients during the second treatment.

In some patients, a third or fourth treatment may be necessary. This is based on clinical evaluation of the disappearance of the tumour. Failure of treatment may be due to mixed patterns in basal cell carcinoma. Other forms of treatment, such as surgery, should then be considered.

Follow up

It is important to inform patients that, because recurrence is possible, routine skin checks are mandatory following successful initial clearance of skin lesions with PDT.

Conclusion

Photodynamic therapy is a huge step forward in the treatment of superficial skin cancers. Previously, patients would have been treated by surgery, with fairly major excisions potentially causing marked scarring. Photodynamic therapy achieves excellent cosmesis with relatively few side effects. In this respect, it is akin to the topical immunomodulator imiquimod, which also achieves excellent cosmesis, but PDT does not rely on patient compliance as it is clinician operated. More research is necessary to determine variables such as optimum wavelength, duration and intensity of light sources and number of treatments. With further improvements, PDT may surpass current therapies as first line treatment for certain skin cancers and dermatoses. MT

Further reading

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DECLARATION OF INTEREST: Dr Pua: None. Professor Barnetson is a member of the Galderma Australia Metvix Advisory Board.

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