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Clinical efficacy of methyl aminolaevulinate photodynamic therapy in basal cell carcinoma and solar keratosis

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INTRODUCTION

According to the National Cancer Control Initiative's National Non-Melanoma Skin Cancer Survey, in 2002, an estimated 256 000 Australians (884/100 000) were treated for basal cell carcinoma (BCC) and 118 000 (387/100 000) were treated for squamous cell carcinoma (SCC).[1] This represented a 35% rise in BCC rates, and a 133% rise in SCC rates since 1985.

Approximately 50% of BCC occur on the head and neck (where cosmetic outcome is important), 27% occur on the trunk (where poor scarring is a common outcome), 13% on the upper limbs and 8% on the lower limbs (where poor healing is a common problem). Some three-quarters of BCC (73%) and SCC (79%) are treated using surgical excision, and the majority are treated in the primary care setting.[1]

Solar keratoses (SK) are very common in the Caucasian population, developing in 7–19% of Australians aged 40 years and over annually. This reflects a significant disease burden.

The risk of progression of SK into invasive SCC is somewhat debated, with rates varying from 0.025% per year[2] to more than 10% per year.[3] Likewise, the risk of regression/remission has not been extensively studied; placebo-controlled studies suggest that at least 20% resolve spontaneously.[4,5] It is without doubt, however, that the majority of SCC (at least 60%) arise from a lesion diagnosed clinically as SK.[6,7]

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) using methyl aminolaevulinate 160 mg/g cream has recently been approved in Australia 'for the treatment of thin or non-hyperkeratotic and non-pigmented solar keratoses on the face and scalp when other registered therapies are unacceptable, and for the primary treatment of superficial and/or nodular BCC where surgery is considered inappropriate.'

Photodynamic therapy involves the application to the lesion of an agent such as methyl aminolaevulinate (MAL) or 5-aminolaevulinic acid (ALA), which is converted by the body to a photoactive porphyrin. Some time later, light of an appropriate wavelength is applied to the skin, creating reactive oxygen species, predominantly singlet oxygen, which results in destruction of the lesion. Red light is used because of the depth of penetration that it can achieve (Fig. 1).

Photodynamic therapy cannot be used for all patients: it is not recommended in pregnancy, breastfeeding or in patients with porphyria, and it does not work well for morphoeic BCC.

The benefits of PDT are that it is relatively selective (thus preserving healthy tissue), non-invasive, has an excellent cosmetic outcome with minimal scarring, and allows multiple lesions to be treated during the same session.

Clinical experience with methyl aminolaevulinate photodynamic therapy

Basal cell carcinoma

Two studies in Australia and the USA have compared nodular BCC complete response rates (histologically verified lesion disappearance at 6 months after the last treatment cycle) with MAL PDT and placebo PDT. (Studies 307 and 308)[8,9]

Patients underwent two treatment sessions 1 week apart, and were then assessed at 3 months. If there was a complete clinical response at 3 months, the lesion was followed for a further 3 months; a second treatment (and further review 3 months later) was undertaken if there was 50–100% reduction in the lesion size, and in cases of no response (i.e. less than 50% improvement), the lesion was excised.

Overall, the histological complete response rate for MAL PDT was in the 70–80% range; although not statistically significant, the lesion complete response rate on the face and scalp was higher than on the trunk, which again was slightly higher than the extremities. In the Australian study, as tumour depth increased efficacy diminished; in the USA, where debulking was somewhat more aggressive, no loss of efficacy with increasing depth was observed. However, this finding does suggest that the procedure may be best used for thin nodular BCC.

Cosmetic outcome was rated as excellent or good by 95% of investigators and patients in the Australian study, and

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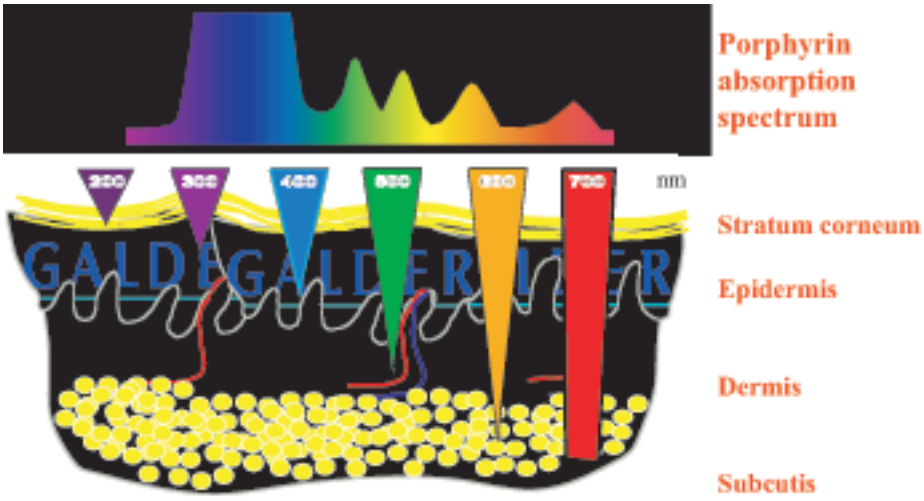

Figure 1 The relationship between light wavelength and skin penetration.

93% in the USA study. Twenty-four of the 31 patients who received MAL PDT had previously been treated for skin cancer; these patients overwhelmingly preferred MAL PDT therapy to their prior treatment.

In an ongoing study comparing MAL PDT (repeated at 3 months in cases of non-response) with excision with a margin at least 5 mm in nodular BCC, lesion complete response rates were approaching those of surgery at 3 months (48/53 (91%) *vs* 51/52 (98%)). Two lesions recurred in the first 12 months, and three in the second 12 months after MAL PDT, compared with two recurrences at 24 months with surgery. Again cosmetic outcome was superior for MAL PDT.[10] These are interim findings from a 5-year study; the longer-term results are awaited with interest.

In superficial BCC, MAL PDT has been compared to cryotherapy with lesions receiving cryotherapy (double freeze–thaw), repeated at 3 months for non-complete responses, or a single PDT session, with two sessions 3 months later for non-complete responses. At 3 and 12 months the complete response for MAL PDT (97%) was at least equivalent to cryotherapy (95%). The 24-month complete clearance rates are at least 80%; further data are awaited. Cosmetic outcomes overwhelmingly support MAL PDT in this study.[11]

In a study of MAL PDT in patients at risk of surgical complications (e.g. oedematous legs, warfarin therapy), there was a 100% complete response for all 20 lesions, with no recurrence at 12 months (Unpublished, Galderma/Photo Cure, data on file, 2000).

Solar keratoses

Three large studies have assessed MAL PDT in SK. A large randomized trial in Europe compared single-cycle MAL PDT (with treatment repeated at 1 week for lesions not on the face or scalp) with cryotherapy double freeze–thaw (mean treatment time of 25 s). Efficacy assessed 3 months after treatment was 69% for PDT and 75% for cryotherapy.[12]

The Australian study treated only face and scalp lesions with two cycles of PDT 1 week apart, single-cycle cryotherapy (mean treatment time 12 s) or placebo. Overall, the complete response rate for MAL PDT was 91%, compared with 68% for cryotherapy ($P < 0.001$) and 30% with placebo ($P < 0.001$).[13] Again the cosmetic outcome favoured MAL PDT over cryotherapy.

In a double-blind, placebo-controlled trial in the USA, the complete lesion response rate for MAL PDT was 89% compared with 38% for placebo ($P = 0.001$). The cosmetic outcome was excellent or good in at least 90% of MAL PDT patients, and most patients rated MAL PDT as more satisfactory than previous treatments.[14]

When the results of these studies and some more recent data are pooled, analysis shows that 77% of lesions respond to a single cycle of PDT. The response rate increases to approximately 90% with two treatments, which compares favourably with cryotherapy (71%). These pooled data also demonstrate that patients prefer MAL PDT to previously received treatments. MAL PDT appears to be better in terms of cosmetic outcome than cryotherapy.

With regard to adverse events in the MAL PDT clinical trials, the most common local adverse events, reported by at least 5% of patients, was a predictable, localized phototoxic reaction, with a burning sensation while undergoing treatment, which tended to settle within a few minutes of treatment cessation, or at worse within 24 hours. Erythema persists for up to 7 days; other reactions are very uncommon.

In conclusion, PDT is a simple, doctor-controlled procedure (which ensures patient compliance) with an established treatment protocol and which allows multiple lesions to be treated during the same session. It is well tolerated, with predictable local phototoxic adverse events, high patient acceptance and superior cosmetic outcome.

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