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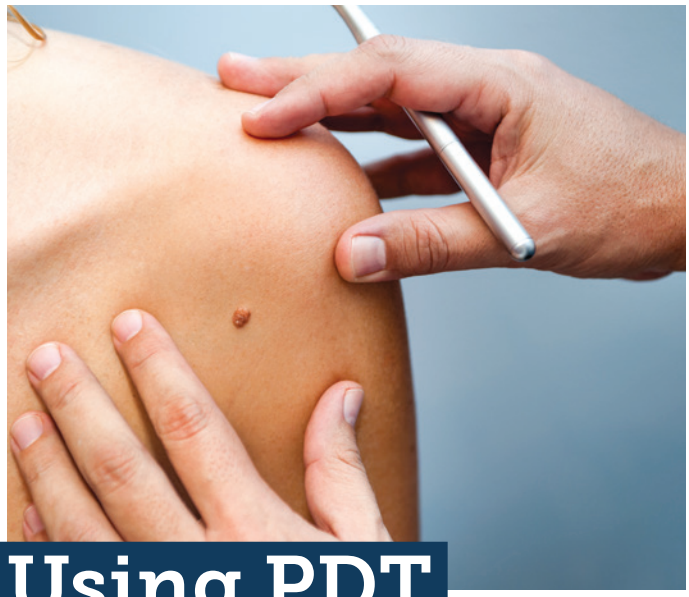

Using PDT

Aesthetic and dermatology nurse prescriber Anna Baker discusses the literature on topical photodynamic therapy for non-melanoma skin cancer with methyl aminolevulinate (MAL)

Introduction

Topical photodynamic therapy (PDT) is a widely used non-invasive treatment for certain non-melanoma skin cancers, permitting treatment of large and multiple lesions with a high safety and efficacy profile as well as excellent cosmesis. This paper will allude to the increasing burden of non-melanoma skin cancer, as well as the licensed indications using MAL PDT for treating actinic keratosis, squamous cell in situ (Bowen's disease), superficial and nodular basal cell carcinoma, and some of the emerging dermatological indications.

Skin cancer prevalence

Non-melanoma skin cancer occurs most often on areas of skin that have been exposed to the sun. Whilst skin cancer in England is less common in people living in the most deprived areas,[1] around 98,400 cases of non-melanoma skin cancer were registered in 2011 in the UK. Registration is incomplete, however, with an estimated 30-50% of basal cell carcinoma (BCC) and around 30% of squamous cell carcinoma (SCC) going unrecorded.[1] Furthermore, approximately 72,100 new cases of non-melanoma skin cancer were reported in the UK in 2013, though it is likely that this underestimates a true incidence.[1] Equally, challenging myths on sun exposure and motivating patients to change unhealthy sun behaviour is an important role and responsibility in clinical practice.[2] The new NICE guidance on sun exposure, released this year,[3] gives evidence-based public information to help prevent skin cancer, and to also ensure the public understand that sensible sunlight exposure is important for vitamin D production.

MAL topical photodynamic therapy

PDT for dermatological indications was first described more than 20 years ago.[4] Topical photodynamic therapy involves the application of a photosensitizing drug to a lesion, which is converted by the haem biosynthetic pathway predominantly to protoporphyrin IX (PpIX) and activated by light of an appropriate wavelength to produce reactive oxygen species, in particular singlet oxygen, which results in apoptosis and necrosis of target tissue.[5] PDT can decrease expression of p53, a marker of early skin cancer,[6] supporting its preventive indication in carcinogenesis.[6] Methyl aminolevulinate 160mg/g MAL (Metvix) cream is licensed for thin, non-hyperkeratotic actinic keratoses (AKs), Bowen's disease (BD), superficial and nodular BCCs (sBCC & nBCC),[8] and is supported by NICE interventional procedure guidance (IPG155).[7] MAL is contraindicated in individuals with a hypersensitivity or allergy to arachis oil, soya, as well as those with a history of porphyria.[8] It is not indicated for treatment of morpheaform basal cell carcinoma.[8] AKs require one treatment, followed by specialist review at three months,[4] whereas BD, sBCC and nBCC require two treatments with a seven-day interval and subsequent specialist review at three months.[4]

Prior to topical application of MAL to the affected lesion/area, it is necessary to remove overlying scales and crusts from the lesion and to slightly roughen the surface to enhance penetration of the photosensitizer.[9] This can be performed with a ring curette or scalpel in a manner insufficient to cause pain and thus not requiring local anaesthesia.[9] MAL is applied to a depth of approximately 1mm thickness and surrounding 5/10mm of skin, which is then covered with an occlusive dressing and photo-protective dressing for three hours. This is to prevent exposure to ambient light during the three-hour incubation period, which may lead to increased activation of PpIX superficially, and potentially reducing deeper photosensitizer penetration before photoactivation.[10] The dressings are then removed and the lesion cleaned with saline. The use of a Wood's lamp following the three-hour application time of the photosensitizer can assist in delineating the boundaries of the lesion by demonstrating photofluoresence; this also indicates the level of uptake of MAL in the lesion, which can be visualised as a coral pink appearance.[11] The lesion is then subjected to red narrowband, which matches the 630/635nm activation peak of PpIX with improved tissue penetration[9] to provide a total dose of 37j/cm2. A Wood's lamp may also be utilised at the end of illumination to assess the extent of photobleaching, (which occurs when MAL has been taken up during the illumination phase of treatment).[10] Tyrrell *et al* (2010) indicate that the extent of

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photobleaching during PDT, as opposed to photofluoresence, is predictive of the level of lesion clearance.[11]

Pain and burning sensation during the illumination component of PDT is widely reported in the literature.[10,12] The sensation can widely vary in intensity and can be influenced by a number of factors, including skin type and anatomical location, as well as the size of lesion (isolated or large area).[10,12] The mechanism behind the discomfort with MAL PDT has not been definitively proven and it has been hypothesised that possible nerve stimulation and/or tissue damage by reactive oxygen species may be the principle cause.[13,14] In addition, the second treatment of a two-therapy cycle may be more uncomfortable.[15] A number of studies analysing the benefit of topical anaesthetics (tetracaine gel and morphine gel) have not been shown to reduce pain significantly during PDT.[16,17,18] Cold-air analgesia and cool water spray are frequently adopted to minimise discomfort during illumination,[10,19] as well as nerve blocks for large field treatments.[20] Erythema and oedema are common post PDT, with crust formation and healing taking place between two to six weeks following treatment,[10] with localised sensitivity that can persist for up to 48 hours post treatment and MAL-induced PpIX clearing from normal skin within 24-48 hours.[21]

Actinic keratosis

AKs are keratotic lesions occurring on chronically light-exposed adult skin.[22] They represent focal areas of abnormal keratinocyte proliferation and differentiation that carry a low risk of progression to invasive SCC.[23] A spectrum of histology can be seen but the poignant feature of an AK is epithelial dysplasia, which may be restricted to the basal layer or may extend to full-thickness atypia, at which point differentiation from BD can be difficult.[12] Histological variants of AK have been described, including hypertrophic, bowenoid, lichenoid, acantholytic and pigmented.[22] AKs are widely considered to be premalignant lesions with low individual potential for invasive malignancy and higher potential for spontaneous regression.[24] They present as discrete, sometimes confluent, patches of erythema and scaling on predominantly sun-exposed skin, usually in middle-aged and elderly individuals, and may be single or multiple in presentation. Chronic exposure to ultraviolet light induces mutations in key genes associated with skin cancer formation, including p53 and deletion of the gene coding for p16 tumour suppressor protein.[25] In addition, UV light also causes immunosuppression which appears to increase human papilloma virus (HPV) expression.[1] Organ transplant recipients as well as those who have been exposed to arsenic are also at a higher risk of developing AKs.[26] Diagnosis of AKs is frequently made on clinical appearance alone, but as the differential diagnosis can include superficial BCC, BD, as well as SCC, a skin biopsy should be performed in cases where there is clinical doubt or suspicion of invasive malignancy.[27] Current European consensus endorses PDT as effective for both lesion and field directed treatment for AKs and suggests that PDT has an especially useful role where AKs are multiple or confluent, at sites of poor healing, or where there has been a poor response to topical therapies.[22] Serra-Guillen *et al,* (2011) undertook a randomised comparison of patient tolerance to MAL-PDT against topical imiquimod for multiple face/scalp AKs and concluded that a significantly higher level of satisfaction was observed following PDT.[28] In addition, a large randomised intraindividual study of face/scalp AKs of 199 patients compared MAL PDT with cryotherapy, which demonstrated that PDT cleared more lesions following the first cycle (87% vs. 76%), but with equivalent outcome after non-responders were retreated (89% vs. 86%).[29] Efficacy for PDT on acral sites has been shown to be reduced by approximately 10% for face/scalp lesions, potentially due to a higher proportion of less-responsive thicker lesions on these sites.[10] Skin field cancerization, the presence of multiple non-melanoma skin cancers, AK, dysplastic keratinocytes in sun-exposed areas, reflects the presence of multilocular clinical and subclinical cancerous lesions.[10] Field therapies, including PDT, are most appropriate for treating field cancerization.[19] A growing body of current literature reinforces the safety and efficacy of MAL daylight PDT, licensed for thin and non-hyperkeratotic AKs.[30] This licensed clinical protocol utilises daylight to activate PpIX instead of narrowband red light. Following at 24-week randomised, controlled, investigator-blinded study comprising 100 subjects, Rubel *et al.,* (2015) concluded that daylight-mediated PDT was not inferior in efficacy to MAL PDT, better tolerated, nearly painless and more convenient for patients.[31] Consensus literature concludes that in view of the reduced accumulation of protoporphyrin IX (PpIX), this results in a significantly lower incidence of pain.[31]

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Superficial and nodular basal cell carcinoma

Basal cell carcinoma is a slow-growing, locally invasive malignant epidermal skin tumour which frequently affects Caucasians.[32] The tumour infiltrates in a three-dimensional manner, through an irregular growth of subclinical finger-like outgrowths which remain contiguous with the tumour mass.[33,34] Metastasis is rare, and morbidity results from local tissue invasion and destruction, particularly on the face, head and neck.[35] Clinical appearances and morphology are diverse, and include nodular, cystic, superficial, morphoeic (sclerosing), keratotic and pigmented variants.[32] Common histological subtypes include nodular (nBCC), superficial (sBCC) and pigmented forms, in addition to morphoeic, micronodular, infiltrative and basosquamous variants, which are particularly associated with aggressive tissue invasion and destruction.[36] In the context of the licensed indications for MAL PDT, nBCC and sBCC will be the focus of this paper.

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Chronic exposure to ultraviolet light induces mutations in key genes associated with skin cancer formation

BCC is the most common cancer in Europe, Australia and the US, and is showing a worldwide increase in incidence.[32,10] Inconsistent data collection does not allow for accurate figures pertaining to the incidence of BCC in the UK.[32] The age shift in the population has been accompanied by an increase in the total number of skin cancers, with a continued rise in tumour incidence predicted up to the year 2040.[37] The most significant aetiological factors appear to be genetic predisposition and exposure to ultraviolet radiation.[9] The sun-exposed areas of the head and neck are the most commonly involved sites.[33] Sun exposure in childhood may be particularly relevant and increasing age, male sex, fair skin types (Fitzpatrick I and II), immunosuppression and arsenic exposure are other recognised risk factors, as well as a diet with a high fat intake.[38,39] Multiple BCCs are a feature of basal cell naevus (Gorlin's) syndrome.[34] Following development of a BCC, patients are at a higher risk of developing subsequent BCCs at other sites.[32] Clearance rates are reported as 92-97% for sBCC when treated with MAL PDT,[10,40] with recurrence rates reported at 9% during the first year following two cycles of treatment.[40] Clearance at three months of 91% of primary nBCC following MAL PDT is reported with 76% clearance consistent at five years.[10] Comparison of MAL PDT with cryotherapy for sBCC were achieved with 96% clearance, with superior cosmesis to cryotherapy.[10] MAL PDT was equivalent to surgery (92% vs. 99%) initial clearance, and 0% recurrences at one year for sBCC, but inferior to surgery for nBCC when recurrence rates were compared (91% vs. 98% initial clearance, 14% and 4% recurrences at five years).[40] Cosmetic outcome was superior following PDT compared with surgery.[10] Topical PDT is best considered for nodular lesions where surgical excision is relatively contraindicated, or where patient preference, reflecting past therapy history, comorbidities and/or cosmetic considerations result in a willingness to accept higher risk of recurrence.[10] It is currently recommended that patients receiving topical PDT for nodular BCC are reviewed for evidence of recurrence for at least one year.[10]

Squamous cell in situ (Bowen's disease)

BD is a form of intraepidermal (in situ) SCC, originally described in 1912.[41] It clinically presents as a gradually enlarging, well demarcated, erythematous and hyperkeratotic plaque with an irregular border,[42] characterised by full-thickness epidermal dysplasia on histology.[9] An annual incidence of 15 per 100,000 has been suggested in the UK; which has been previously based on US data, which may reflect a higher incidence due to greater sun exposure.[9] In the UK, the peak age group for BD is the 70th decade, with approximately 75% of cases occurring on the lower leg predominantly in women (70-85% of cases).[42,43] More recent data indicates the most commonly affected sites are the head and neck (29-54%).[44,45] Lesions are usually solitary but are multiple in approximately 10-20% of patients.[46] Less common sites or variants include pigmented BD, subungual/periungual, palmar, genital, perianal and verrucous SCC in situ.[42] In cases of clinical diagnostic doubt, a punch biopsy can be performed to establish the full thickness of the epidermis and dermis to ascertain the presence of any invasive disease amounting to a cutaneous SCC.[9] Aetiological factors of BD include: irradiation (ultraviolet radiation, solar iatrogenic and sunbeds) and radiotherapy, carcinogens (arsenic), immunosuppression (particularly therapeutic), viral (there is an association between human papillomavirus HPV, especially HPV16, and the development of anogenital SCC in situ).[9] Current literature indicates clearance of 86-93% of BD lesions, three months beyond two cycles of MAL PDT using red-light, with sustained clearance at 24 months of 68-71%, equivalent to conventional therapy, but with superior cosmesis.[9,10] Therapy guidelines recommend PDT as the treatment of choice for both large and small plaques of BD on poor healing sites, representing the majority of lesions, and a good choice for larger lesions in good-healing sites.[9]

Novel indications

PDT has been studied extensively in acne, yet a consensus protocol has yet to be determined. Follicular obstruction and congestion may be reduced by enhanced epidermal turnover promoted by PDT.[10] Propionibacterium acnes (p.acnes) naturally produce small amounts of endogenous porphyrins[47] yet, the literature is mixed in determining a consistent reduction, or temporary reduction in p.acnes following PDT. A decrease in sebum excretion has been more consistently noted.[47] Red light has been shown to possess greater potential in sebaceous gland destruction, when compared to blue and pulsed light, but treatment was noted to be more painful using a conventional MAL protocol of a three-hour application time.[12] A growing number of studies increasingly acknowledge the potential photorejuvenation component of PDT, with findings indicating observed improvement in fine wrinkles, mottled hyperpigmentation, roughness and sallowness, as well as upregulation of collagen production and increased epidermal proliferation.[48,49]

Conclusion

The current license(s) for MAL PDT only extend to the indications previously discussed; it is not recommended for thick/nodular BCC or SCC. Treatment is contraindicated for morpheaform BCC, porphyria and in individuals with a peanut allergy due to the arachis oil. PDT is most efficacious in lesions that have been well prepared with excess keratin removed/softened to allow for optimum absorption of MAL. MAL topical PDT provides a safe and efficacious treatment modality for certain non-melanoma skin cancers. The procedure can be repeated as often as required and may be especially suitable for patients with large areas/field cancerization. The novel and licensed indications discussed are by no means exhaustive and continue to expand, demonstrating the evolving potential for this innovative treatment. The future is bright for topical PDT!

Anna Baker is a dermatology and cosmetic nurse practitioner, running nurse-led Topical PDT clinics for Galderma UK in conjunction with Ashfield Clinical. She works alongside Mr Dalvi Humzah as the coordinator and assistant tutor for Facial Anatomy Teaching. Baker has a post-graduate certificate in applied clinical anatomy, specialising in head and neck anatomy.

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