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The Adverse Effects of Topical Photodynamic Therapy: a consensus review and approach to management

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Topical photodynamic therapy (PDT) is widely used to effectively treat superficial non-melanoma skin cancer and dysplasia. As with any therapeutic approach, the risk/benefit profile must be taken into account on an individual patient basis; in general, PDT is well tolerated. Historically, PDT-induced pain has been a potentially limiting factor, but with optimisation of treatment parameters, such as the introduction of lower irradiance regimens, pain is now uncommonly a major issue. Expected "adverse" effects of a phototoxic insult also include inflammation, manifest as erythema, exudation and sometimes urticaria. Other side-effects are uncommon and include scarring, altered hair growth or pigmentary change and allergic reactions. The theoretical risk of carcinogenesis with cumulative PDT treatments is unproven and indeed PDT can be considered as a prophylactic approach in high-risk patients, such as the immunosuppressed. This review summarises the current evidence relating to the adverse effects of topical PDT as part of the guideline updating project on this subject[1] and attempts to interpret this evidence in the context of patient risk (Table 1).

1.1 Pain

1.1.1 Characteristics and frequency

PDT exerts its effects through a phototoxic mechanism, and as part of this, pain and inflammation occur. With some of the more conventional higher irradiance topical PDT regimens, pain during irradiation is almost invariable. The mechanisms of PDT-induced pain are poorly understood but studies in an adenocarcinoma cell line *in vitro* demonstrated preferential uptake of 5-aminolevulinic acid (ALA) by beta-amino acid and GABA transporters, which was not seen with methyl aminolevulinate (MAL); this may be one possible explanation for the neurogenic nature of the pain experienced during ALA-PDT, although this was in a cell line model and has not been substantiated in humans.[2] In contrast, MAL uptake has been shown, in a human colon adenocarcinoma cell line, to be mediated by active transport mechanisms

involving non-polar amino acids, providing a potential rationale for any differences in pain mechanisms and experience during PDT following photosensitisation by either ALA or MAL.[3]

Whilst there have been only limited studies of the mechanisms of PDT in human skin, it is clear that there is oxidative stress and generation of reactive oxygen species, and an inflammatory reaction involving release of histamine, nitric oxide, prostaglandin PGE_2, TNF-alpha and other cytokines, and these may also be implicated in the pain and discomfort during and following PDT.[2,4-6] In addition, a neurogenic mechanism involving TRP receptors has been implicated.[7-9] A recent study also showed mechanistic differences between ALA and MAL, in that ALA-PDT appeared to induce pain via singlet oxygen-mediated lipid peroxidation, in turn triggering nociceptor activation via TRPV1 receptors in dorsal root ganglia *in vitro*. Furthermore, the TRPV1 inhibitor, menthol, reduced action potentials evoked by ALA-PDT in dorsal root ganglia and pain behaviour in a mouse model, although this was not the case with MAL-PDT.[10]

In humans, PDT-induced pain commences almost immediately after irradiation starts. Commonly, patients describe a prickling, stinging, sharp burning sensation, most similar to that reported by patients with erythropoetic protoporphyria.[11,12] There is large inter-individual variation in the degree and nature of PDT-induced pain experienced by patients, although approximately 16% to 20% will report severe pain with conventional PDT.[13-16] The multifactorial nature of PDT-induced pain and relative limitations of effective treatment options are well described.[17] In one study which looked retrospectively at experience related to almost 1000 PDT treatments, 44% of patients required some form of pain-reducing intervention.[18] Indeed, in two separate studies, one a survey of PDT services in Scotland and the other a prospective cohort study, of patients treated with PDT for superficial BCC, SCC *in situ* or AK, 28% to 38% of patients reported moderate to severe pain (score over 6 on a 0-10 numerical rating scale).[19,20] Most of these data are derived from conventional topical PDT regimens using hospital-based,

relatively higher irradiance light delivery. However, the PDT procedure is generally very well tolerated, with the pain in the majority of cases resolving once the irradiation period ends (7-9 minutes with the most widely used red LED source) and this is reflected in patient preference for PDT over alternative treatments. Nevertheless, the potential for this degree of pain is not ideal for patient care, and thus, information on predictive factors and suitable methods of pain relief are required.

1.1.2 Predictive factors of PDT-induced pain

Patient, lesion and treatment site characteristics

The literature relating to possible predictors of PDT-induced pain is complicated by the fact that many of the studies reported are retrospective and have multiple confounding factors. There are conflicting reports of an impact of gender and skin phototype but there is no clear pattern emerging to suggest a strong effect of age, sex or skin phototype on likelihood of severe pain experienced with topical PDT.[13,18,20-24] More consistently, there is evidence to support PDT to larger treatment areas being associated with more pain;[13,14,16,18,22,23,25] therefore, this has the potential to limit the size of field that can be treated with conventional PDT, although the increasing use of daylight PDT (dPDT) has been beneficial in this regard.[26] Any possible influence of diagnosis and body site is not clear, again due to potential confounders as, for example, AK tend to affect larger areas and arise on the head and neck. However, reports of PDT used for AK when compared with BCC,[27] acne,[28,29] psoriasis[30,31] and viral warts[32,33] indicate that higher PDT-induced pain scores may be observed when treating these conditions. Thus, it is important to have an awareness of this to minimise any potential impact on treatment delivery and to ensure that patients are appropriately advised and managed.

One study also indicated that there was an association between more severe pain and the degree of erythema in the pre-treated lesion.[14] However, this association has not been found by

other investigators.[21] Likewise, whilst Lindberg *et al.* reported that the second treatment was more painful than the first in 38 patients treated with PDT[34] it has, again, not been confirmed by other investigators.[16,21,35] The study of Sandberg *et al.* also showed that lesions that responded best to PDT were associated with more pain,[14] and it may be intuitive to consider that the more photosensitiser uptake and the greater lesional fluorescence and subsequent phototoxic insult, might well lead to the best therapeutic outcome. However, this is not the case when treating AK on the dorsal hands with PDT, as increasing protoporphyrin IX (PpIX) accumulation does not improve efficacy of treatment but increases adverse effects.[36] Sub-group analysis of the larger, multicentre, randomized controlled trials (RCTs) of efficacy of PDT, particularly in dysplasia and superficial NMSC, have not been undertaken to investigate whether there is an association between fluorescence,[37] phototoxic inflammation and subsequent therapeutic outcome.[37] Certainly, there is some evidence in smaller studies of a correlation between the degree of fluorescence intensity and pain experienced during PDT, and this has been shown in acne vulgaris[28,38] and in AK. In the latter study, the association with pain was shown between both the degree of PpIX fluorescence and the fluence rate of light delivery, and this is supported by other investigators.[16] Furthermore, pain is not required for PDT efficacy as exemplified by dPDT, which is considered to be due to the lower irradiance of daylight and of low level of continuous photoactivation of PpIX.[39]

The influence of prodrug on PDT-induced pain

In a double-blind, RCT investigating forearm sites in healthy volunteers which had been tape-stripped, pain was higher on sites exposed to ALA than MAL. In addition, ALA induced higher levels of fluorescence, and there was a greater decrease in fluorescence with irradiation.[38] In a separate study, the same group compared the pain associated with MAL-PDT with ALA-PDT for acne and AK, and showed that the pain experienced was greater with more intense PpIX fluorescence and with a higher rate of light delivery.[40] This greater level of PpIX accumulation

and fluorescence associated with ALA has consistently been reported, both in normal skin[41,42] and diseased skin.[28] In addition to higher levels of phototoxicity occurring in normal skin following ALA-PDT compared with MAL-PDT, more prolonged hyperpigmentation may also occur with the former.[43] However, when analysing studies in which MAL-PDT and ALA-PDT have been compared directly, usually there have been other variables, in particular the duration of application of the prodrugs.[44,45] Indeed, two small studies comparing ALA-PDT and MAL-PDT when used for nodular BCC and acne with application for 3 hours in each, showed no differences in acute pain scores between the prodrugs,[28,46] although there was greater pain associated with ALA-PDT at 24 hours post-treatment in the acne study.[28] More recently, in a large, multicentre study comparing ALA in nanocolloid emulsion (BF-200 ALA) with MAL-PDT, there was no significant difference in adverse effects seen between the prodrug treatment arms.[47] Reduction of drug concentration and/or incubation time may also be considered for effective, less painful PDT, as may be employed for AK or acne.[48-50] With the development of newer formulations of topical prodrugs and lower drug dose regimens, vigilance is required to ascertain whether any change in depth of effect and efficacy may also be associated with changes in pain experienced and tolerance of treatment.[51-53]

The influence of light delivery on PDT-induced pain

Most topical PDT is undertaken using LED light delivery. There are few studies in which laser light delivery has been compared with non-coherent broadband light sources, although the evidence from two studies, one of which was retrospective, indicated no significant difference in efficacy or adverse effects, which included pain.[11,54] Certainly, *in vitro* and *in vivo* studies support the safety profile of LED light delivery.[55,56] Čarija *et al.* undertook a within-patient, prospective, controlled study of LED-PDT with pulse dye laser-PDT in 15 patients with 62 BCC lesions.[57] Whilst there were similar pain scores between the treatment arms, lower clearance rates were seen at 12 months with pulse dye laser-PDT.

In the large, multicentre study comparing BF-200 ALA- and MAL-PDT for AK,[47] more adverse effects were observed in patients treated with a narrower spectrum LED source than in those treated with a broader spectrum, albeit without longer-term safety concerns.[58] Investigators have shown that variable pulsing of light delivery may reduce the pain associated with MAL-PDT for AK in a prospective, controlled study that also showed no loss of efficacy or change in patient satisfaction.[59] Other variables of light delivery have been studied, including the use of filtering of infrared in one study of 80 subjects, which was associated with less pain than conventional LED PDT, without loss of efficacy.[60]

Most dermatological PDT uses red light for delivery of depth of effect but the wavelengths included do impact on PDT-induced pain. In one AK study where green and red light PDT were compared, less pain was experienced using the former with no loss of efficacy in this superficial indication.[61] However, a similar study comparing green and red light for SCC *in situ* showed loss of efficacy with green light and no significant difference in pain.[62] Mikolajewska *et al.* undertook a study in ten healthy volunteers exposed to topical ALA and MAL for 24 hours and irradiation was undertaken using either violet laser light or red laser light.[63] In this study, greater pain was experienced in association with red light and a more persistent erythema seen for ALA-PDT, although these differences were not seen in the sites treated with MAL-PDT. However, the results have not been followed up with investigations in diseased tissue and the relevance of this in the clinical setting is unclear. There does not seem to be a strong association between pain experienced during PDT and the total light dose used,[64] and this is likely reflecting the fact that pain is maximally experienced in the first half of irradiation.[64-66] Thus, simply reducing the total dose used is unlikely to impact significantly on the tolerance of treatment.

However, there is substantial evidence that lower irradiance light delivery during PDT, such as dPDT or reduced irradiance hospital or portable device light delivery, is at least as effective as conventional higher irradiance regimens.[37,39,40,67-72] It seems that at lower irradiances, particularly <50 mW/cm^2, less pain is experienced during PDT.[7,39,40,67-69,73-76]

In particular, the use of dPDT has been compared with conventional PDT in large, within-patient, multicentre studies, most recently in Europe and Australia involving patients with mild to moderate field change AK.[77,78] An overall consensus indicates that dPDT to large areas of AK is extremely well-tolerated, with much lower pain scores than for conventional PDT, and that efficacy rates are similar.[70] In addition, in support of the use of low irradiance PDT, preliminary data obtained from non-comparative, open studies of low irradiance portable ambulatory LED devices[37,71,72] indicate that pain scores are also very low and efficacy at 1 year follow-up is high.[79]

These are important developments for the use of PDT in situations where pain previously could have been a treatment-limiting factor. This now enables larger areas to be treated in a well-tolerated and an almost painless, effective regimen with dPDT. Another alternative means of varying irradiance using conventional hospital-based LED devices is with use of an initially reduced irradiance at less than 50 mW/cm^2, and thereafter, for the latter part of the regimen, to increase irradiance in order to deliver an overall effective light dose. This approach of increasing irradiance during PDT after an initial lower (<50mW/cm^2) irradiance approach to light delivery may be associated with reduced pain scores and can be useful for example if treating genital or perineal sites.[80] This was investigated in a retrospective, single-arm study of 14 patients treated with this two-step irradiance regimen for BCC and SCC *in situ*, showing high clearance rates.[81,82] Fractionation of light has also been investigated as a means of improving efficacy of

PDT,[83] although this has been shown to be at the expense of increased adverse effects, notably pain.

Pain – how does PDT compare with other treatments?

When looking at the outcome of severe pain which requires a break in treatment or use of local infiltration anaesthesia, PDT results in significantly higher pain scores compared with placebo.[29,47,84,85] This is also the case for lower levels of more manageable pain. Furthermore, when comparing dPDT with conventional PDT, the former is significantly less painful, based on large, multicentre studies.[39,70,73,77,78]

In the larger studies comparing the outcome of severe pain which requires a break in treatment or use of local infiltration anaesthesia, no significant differences were seen between cryotherapy, 5-fluorouracil or imiquimod,[35,86-88] whereas less pain was experienced with surgical excision than with PDT, although this would be expected as local anaesthesia is used for the surgical procedure.[89] Of note, the pain and discomfort of other topical treatments, such as 5-fluorouracil or imiquimod, is not directly comparable with PDT; the former are associated with increasing discomfort and inflammation during the course of treatment, over several weeks, whereas the pain experienced by PDT is maximal in the first few minutes of treatment which then subsides rapidly.[35,90] This is an acute, rather than a more chronic experience, probably indicating why patient satisfaction levels with PDT are high.[91]

Thus, when MAL-PDT was compared with ingenol mebutate for treatment of multiple AKs on the face and scalp in within-patient, split-face studies, pain scores and cosmetic outcome were higher with PDT, but local skin reactions were more severe and persistent with ingenol mebutate; overall, patients preferred PDT.[92,93] When dPDT was compared with ingenol mebutate in 27 subjects with AK in a within-patient study, pain scores were higher for ingenol

mebutate.[94] Similar efficacy was reported between the two groups but increased tolerance for dPDT was documented in terms of reduced local skin reactions and pain, and preference for dPDT.[94]

Furthermore, in a randomized, observer-blinded, within-patient comparison of patients with multiple AKs treated with trichloroacetic acid compared with ALA-PDT, higher pain scores and efficacy rates were seen with PDT and scarring was present only in those treated with trichloroacetic acid.[95]

1.1.3 Pain relief for PDT-induced pain

Treating with methods of no significant benefit

Given the nature of PDT-induced pain and the probable neurogenic mechanisms involved, it may be anticipated that topical anaesthesia could be beneficial for pain relief during PDT. However, in a within-patient, double-blind RCT of ALA for extensive AK on the scalp, Langan *et al.* failed to show a significant effect of eutectic mixture of local anaesthetics (EMLA) for PDT-induced pain.[96] This is supported by observations by Grapengiesser *et al.* in 60 patients in which EMLA was used during PDT.[13] A separate inter-individual study by Holmes *et al.* found no significant effect of tetracaine gel (Ametop®) used topically during ALA-PDT for superficial BCC, SCC *in situ* or AK.[97] Likewise, during large-area PDT for facial AK and field change carcinogenesis, no benefit of topical 3% lidocaine hydrochloride cream was found.[98] In a randomized, double-blind, placebo controlled study, morphine gel 0.3% was shown not to be significantly beneficial for pain relief during topical MAL-PDT;[99] Sandberg *et al.* observed that capsaicin cream was also not significantly effective in reducing pain and there were side-effects of the topical capsaicin itself.[14]

Treating with methods of potential benefit

In contrast, a pilot, open, split-face study performed by *Borelli et al.* on the use of subcutaneous infiltration of 1% ropivacaine with 1% prilocaine for PDT pain relief showed benefit, although there were significant adverse effects of cheek swelling persisting for up to 3 days, which could limit its use.[100] This has been supported in a separate case report showing the benefit of subcutaneous anaesthesia for pain relief during PDT in a 7 year-old child.[101]

In addition, peripheral nerve blockade can be significantly effective in reducing PDT-induced pain when used for extensive facial AK. In an initial study in 16 patients with symmetrical facial AK, nerve blockade using mepivacaine and adrenaline was used to block supra-orbital, supra-trochlear, infra-orbital and mental nerves and the non-anesthetised side served as control. Pain scores were significantly reduced on the anaesthetised side and 15 of the 16 patients expressed preference for nerve blockade in future if PDT was required.[102] This has also been supported by a separate study in 10 males with facial AK using supra-orbital, supra-trochlear and occipital nerve blockade during MAL-PDT.[103] In an open clinical trial involving 34 patients with frontal facial AK where supra-orbital and supra-trochlear nerve blockade was used on one side and cold air analgesia on the other, nerve blockade was significantly superior with respect to pain relief, with preference in 31 of the 34 patients.[104] However, nerve blockade is only possible at certain body sites, and of course, requires an additional invasive procedure, and as such, it may not be appropriate for many patients treated with PDT.

In a prospective, controlled, observational study to address the potential effect of nitrous oxide, involving 71 patients treated with MAL-PDT to multiple AKs on the cheeks, all patients received 800 mg of ibuprofen 30 minutes before PDT irradiation. In addition, cooling was used with a cold air fan and interruptions in treatment were allowed if required and, for patients who experienced severe pain (visual analogue scale, VAS, score of ≥ 6) despite ibuprofen and cooling air,

additional nitrous oxide and oxygen mixture (Livopan®) was offered for PDT to the other cheek. Overall, a reduction in pain score of 55.2% was seen between treatments to the first and second cheek following application of the nitrous oxide and oxygen mixture. Treatment was generally well-tolerated, although 6 of 30 patients (20%) experienced mild side-effects during inhalation of the nitrous oxide and oxygen mix, which included vertigo, fear of loss of control and amplification of noise.[105]

Considering other options for pain relief during PDT, investigators have explored the potential use of transcutaneous electrical nerve stimulation (TENS). This was undertaken in a pilot study in 14 patients with facial and scalp AK who had experienced severe pain during earlier PDT treatments. When the TENS electrodes were placed on the shoulders, four patients found no benefit from the use of TENS, three patients (21%) who had had previous interrupted PDT sessions due to pain were able to complete treatment, although the reduction in pain scores was modest (8.1 – 6.2). Overall, all but one patient would have used TENS again during PDT. This pilot study requires further investigation, although TENS is only feasible at certain body sites and therefore may have limited application in routine clinical use.[106]

In many PDT regimens, use of a cold-water spray is employed as a routine measure during PDT. In a double-blind, controlled study involving 85 patients treated with ALA-PDT for AK or acne vulgaris, two thermal spring waters were investigated and sprayed four times daily to the face for a week following PDT. A reduction in discomfort, pain and erythema was experienced between days two and seven, although no impact was shown on the period of maximal pain, which was on day one.[107] In a separate study in 24 patients with AK treated with MAL-PDT on two symmetrical areas, cooling with either cold water spray or cold water pack was employed in either the first or second period of illumination. The water spray and cool pack reduced mean pain scores modestly by 1.2 - 1.3 points, however, pausing irradiation was associated with a

higher reduction in pain of 3 – 3.7 points. Thus, whilst cooling resulted in minor reduction in pain intensity, a pause in illumination was more effective for pain relief, and these are relatively easy ways that can be incorporated routinely into clinical PDT practice.[108] Pausing during illumination may also be useful when treating acne with PDT.[51] The relatively small impact of cooling air on reduced PDT-associated pain was also shown by Stangeland *et al.* who undertook an open, within-patient, right-left comparison study in 43 patients treated with MAL-PDT for field change cancerisation, showing a small but significant reduction in pain scores in those treated with cold air analgesia.[109] These observations of the utility of cooling are supported by a non-randomized, retrospective, observational, controlled study in which cooling devices were seen to be associated with reduced PpIX photobleaching. However, a reduction in disease clearance rate was seen at 3 months of follow-up and thus cooling should be used with caution because of concerns about adverse impact on therapeutic effect.[110]

Other treatment methods

Less conventional approaches have included a plant-derived spray which contained camomile and menthol, which was used in addition to glycolic acid. A randomized, blinded study involving 56 patients with field change cancerisation of either arm (n=25) or face (n=31) showed reduced pain scores at all time points up to 30 minutes, during and after treatment. The sprays were applied to treatment areas 10 minutes before irradiation and at any time during irradiation, with the placebo being a coffee scented saline spray.[111] Whilst this may be a relatively simple method to reduce discomfort when large areas are treated with PDT, it needs further study.

Whilst PDT is generally well tolerated, exploring options for patients who have found PDT to be painful is worthwhile. A single session of hypnosis was explored in a pilot study of 12 patients treated with PDT for pre-cancerous lesions (actinic keratosis, SCC *in-situ*, Bowenoid papulosis and Paget's disease), showing significantly reduced pain scores in eight patients, six of whom

had previously experienced PDT without hypnosis. Whilst it would not be required for most patients treated with PDT, hypnosis requires further investigation as it could be considered in exceptional circumstances if proven to be effective. A limitation would be the requirement for members of staff to be trained adequately in hypnosis.[112]

Thus, whilst nerve block, subcutaneous infiltration with anaesthetic, TENS, cooling air and/or pausing irradiation may be of benefit, more typical forms of topical anaesthetics or oral analgesics[20,113] have not been shown to be effective. Modifying PDT regimens to employ lower irradiance light delivery is usually most effective, enabling successful treatment.[7,114]

1.2 Phototoxicity of topical PDT

The inflammatory reaction following PDT is expected as a consequence of the phototoxic effect. This usually manifests as erythema and oedema, and sometimes with associated wheal and flare, i.e. an urticarial reaction.[115,116] Persistence of erythema may be seen for some months following treatment.[11] Crusting, infection, sterile pustules and erosions are also uncommon adverse effects.[117]

In a study involving ten healthy volunteers, erythema induced by ALA-PDT peaked at 1-2 hours following cessation of irradiation,[6] although laser Doppler studies[118] have shown that the increase in blood flow that occurs immediately after topical PDT persists for a week. Marked inter-individual variability is seen in phototoxic reaction and there are also body sites effects, with reports of increased phototoxic reactions mid-face,[119] consistent with increased pain at this site.[22] Phototoxic inflammation seems to be greater following the application of ALA rather than MAL. In a randomized comparison of ALA- and MAL-PDT involving 34 healthy volunteers, a composite score of erythema, oedema and pigmentation was significantly greater for ALA-PDT

than for MAL-PDT, which likely reflected the increased pigmentation seen with ALA-PDT, persisting for 4 weeks.[43]

Detailed investigation of ALA-PDT-induced phototoxicity in normal human skin indicated the release of histamine, accompanying an early urticarial phase, although cetirizine showed no effect on the erythemal response at 24 hours.[4] Consistent with this is the occurrence of clinically reported urticaria seen immediately, during and after topical PDT in a small proportion of patients, and possibly being more likely in those with severe photodamage. The incidence of urticaria has been reported to be between 0.9% – 3.8%, and antihistamines may be of some benefit when used prophylactically for itch and wheal.[120,121] Prominent phototoxic erythema, associated with malaise and flu-like symptoms, was recently reported in two organ transplant recipients treated with PDT for photodamage.[122]

Whilst there is significant evidence of an association between prodrug-induced fluorescence, phototoxicity and pain,[21,40,123,124] an association between phototoxicity and therapeutic outcome is less clear-cut. An association between PpIX photobleaching and clinical outcome at 3 months' follow-up following PDT treatment was observed in a pilot study in diseased skin.[125] In a separate study involving 24 healthy volunteers, forearm skin was tape-stripped and during different times of incubation of MAL, fluorescence photobleaching was assessed during red light irradiation. A significant correlation was seen between the incubation time of the prodrug and time to illumination and photobleaching; there was also a significant correlation between photobleaching and erythema, and between photobleaching and pain. These imply that shorter incubation periods of the prodrug may result in reduced pain, although impact on efficacy in diseased skin is unclear.[126] In addition, reduced MAL concentration may also reduce any potential for increased pigmentation.[127]

In a study of 22 patients with field change mild AK on the face and scalp, the application of MAL for 30 minutes compared with MAL for 3 hours, with both sites then irradiated at 3 hours was investigated. The application of a super-potent corticosteroid before and after PDT to the short application, pulsed PDT site was also investigated. The reduction of MAL application time and the use of topical corticosteroid reduced PDT-induced erythema at 24 hours but did not impact on efficacy at 3 months.[128] The same group studied 22 subjects with facial and scalp AK separately and also showed that application of a super-potent corticosteroid reduced the inflammation and erythema of PDT but did not impair efficacy.[129] Furthermore, during dPDT, using light protection of the skin following PDT appears to reduce inflammation, although its impact on efficacy is unclear.[130] It is also of interest to note that brimonidine tartrate gel may also have the potential to reduce erythema following dPDT, although its impact on efficacy, again, is unknown.[131]

Patient satisfaction, tolerance and cosmetic outcome

High levels of patient satisfaction are reported for PDT, although pain may impact on patients' perception of the treatment.[77,78,87,91,132-138] Improved tolerance and satisfaction with PDT was reported in one randomized study comparing PDT with imiquimod for AK[139-141] and improved preference for PDT compared with cryotherapy was reported in a RCT comparing MAL-PDT with cryotherapy for superficial BCC with a 5-year follow-up.[87] MAL-PDT compares favourably with ingenol mebutate when used for AKs on the face and scalp, with superior cosmetic outcomes and an overall patient preference for PDT, due to higher pain scores and local skin reactions being more severe and persistent with ingenol mebutate.[92,93] Similarly, when dPDT was compared with ingenol mebutate in 27 subjects with AK in a within-patient study, the former was better tolerated and preferred, and was associated with fewer adverse effects; efficacy was similar between the two modalities.[94] When comparing trichloroacetic acid with ALA-PDT for

scalp AK, higher efficacy rates and pain scores were seen with PDT and scarring was present only in the trichloroacetic acid-treated subjects.[95]

1.3 Allergic contact dermatitis to prodrugs

Topical PDT induces an inflammatory reaction consisting of erythema, often with some oedema and subsequent crusting; these are expected effects of topical PDT. The degree and severity often reflect the severity of photodamage and the area that is treated. Whilst it could be the development of an irritant dermatitis, the possibility of the patient becoming sensitised and having developed allergic contact dermatitis to the prodrug should be considered, especially with a prolonged and persistent inflammation following PDT.

There are independent reports of allergic contact dermatitis arising to MAL.[142-148] In one study, positive patch testing to MAL cream (but not to placebo) was seen, indicating that this is likely to be due to the prodrug itself and not the excipient.[146] The risk of sensitisation is predicted to be of the order of 1-2%.[145,146] However, it is important to be aware of this possible adverse effect as a more generalised dermatitis can occur if this is not recognised and PDT is continued.[144,149] Contact dermatitis has been reported to MAL and, more recently, to BF-200 ALA.[148]

Reviewing the separate studies, the risk of sensitisation is increased in those patients who have had multiple treatments with PDT and large areas treated. It is important to be aware of and have a low threshold for considering patch testing in patients who develop a more severe or atypical reaction to PDT. With increasing use of dPDT for large-area treatment it would be wise to be vigilant in this patient group.

1.4 Medium-term adverse effects

The relative selectivity of PDT and the observation from large, multicentre studies that healing and cosmetic outcome are good[77,78,87,91,132-138] mean that PDT is often selected as the treatment of choice to use at difficult sites such as lower legs, where healing may be problematic. Whilst changes of fibrosis can be seen histologically following PDT,[150] scarring is rarely reported[77,78,87,91,132-138,151] and indeed PDT has been explored for its use in scar remodelling[152] and potential to treat keloid scar,[153] although this requires further investigation. Rarely, milia cysts may occur following PDT if the basal membrane is disrupted; this may be difficult to distinguish from recurrent BCC[154] but in practice this is an occasional adverse effect.

In early studies of the use of high-intensity PDT regimens for acne vulgaris, biopsy evidence of destruction of sebaceous glands was observed,[155] although current acne regimens are of lower intensity with regard to irradiation. As such, it is anticipated that the risk of permanent damage to sebaceous glands will be lowered, although further studies with histological evidence of this have not been undertaken. Sterile pustules are often reported following PDT for acne vulgaris, although true infection is rarely seen,[28,29] probably because of the anti-infective effects of PDT. Photo-onycholysis is well recognised with drug phototoxicity such as with psoralens[156] and there are isolated reports of photo-onycholysis occurring following PDT when this has been undertaken at periungual sites, such as for viral warts[157] and AK,[158] and even one case arising following blue light ALA-PDT to AK on the face.[159]

Pigmentary problems

Dyspigmentation may occur following PDT although is uncommon; in fact, in the larger trials involving AK, extramammary Paget's disease, warts and acne, no significant pigmentary changes were detected.[51,160-162] Hyperpigmentation[43] may occur which seems particularly likely with darker skin phototypes, and has been seen in the context of using PDT for acne vulgaris.[155,163] However, in light-skinned populations, hyperpigmentation is only rarely seen.[151] It

is also not clear whether combining PDT with any pre-treatment steps may increase the risk of pigmentation. In one study, whilst there was a trend to increased pigmentation with CO_2 laser-assisted PDT, this was not significantly different from PDT alone.[160]

If hyperpigmentation occurs, it is usually reversible over some weeks. In one study, biopsy of PDT-induced pigmentation showed histologically increased numbers of activated melanocytes.[164] Hypopigmentation may also occur, presumably as a post-inflammatory insult, although is rarely a problem clinically.[151]

Hair problems

If PDT is undertaken at hair-bearing sites such as the scalp or beard area, there is potential for hair loss, and this has been observed following PDT treatment of large areas of SCC *in situ* and BCC.[165] However, this is not well reported in the literature but may be worth keeping in mind with regard to warning patients of this potential side-effect at the relevant treatment sites. Paradoxically, topical PDT may also increase hair growth, and one of the early studies of topical PDT was using hematoporphyrin derivative and UVA irradiation as an attempt to treat areas of alopecia areata.[166] Although that initial study was encouraging, subsequent studies have been disappointing, showing no convincing efficacy.[167,168] However, one report of a study in mice indicated that the presence of iron was required with ALA to stimulate hair growth, although this has not been investigated in humans.[169]

1.5 Miscellaneous

Thus, whilst the main adverse effects of PDT are pain, which can usually be minimised through modification of treatment approaches and the expected inflammatory phototoxic reaction, there have been rare reports of other miscellaneous adverse effects. PDT has been used to treat erosive pustular dermatosis, but there are also reports of the development of erosive pustular

dermatosis of the scalp occurring within 1-3 months following PDT treatment of AK of the scalp;[170,171] the possibility that this may be triggered by the insult of PDT exists. Possibly via similar mechanisms, localised bullous pemphigoid developing 3-4 months following PDT has also been observed.[172,173] In the more recent study, the patient additionally developed blistering lesions at non-treatment sites,[173] and in both cases, whilst it is possible to speculate that the trigger may have been PDT, it is not clear-cut and may have been coincidental. Likewise, a case of pemphigus vulgaris developing one week after a third PDT session at an adjacent site raises the possibility of an association, although again, it may have been coincidental as the condition generalised.[174]

The antimicrobial effects of PDT are increasingly being explored and infection following PDT is unusual and less likely than with other topical therapies.[88] Interestingly, despite a report of reactivation of herpes simplex virus at the treatment site, 24-48 hrs following PDT for AK on the forehead,[175] topical ALA PDT has also been investigated in eight patients with recurrent herpes simplex virus infection (oral and genital), with encouraging preliminary data suggesting that PDT may have therapeutic and preventative effects in reduction of HSV recurrence and this warrants further study.[176] There was one report of a peripheral nerve palsy developing 1 week following a second treatment session with MAL-PDT for facial AK (forehead, cheek and jaw).[177] Other causes of facial palsy were excluded, and despite systemic corticosteroids, the patient had no clinical improvement in the facial palsy at 16-month follow-up. Whilst this may have been coincidental, the occurrence on the same side of treatment, just 1 week post-treatment, raises the possibility of causal association; this could be either due to a direct traumatic effect of PDT on the superficial facial nerve branches or through viral reactivation, although there was no evidence of this in this case. There were also four cases reported of cellulitis developing following treatment of AK with PDT.[178]

There was a report of five patients who developed transient memory impairment and global amnesia immediately following PDT for AK.[179] This did not appear to be associated with pain, and the neurological symptoms all resolved without sequelae within 24 hours; the patients were investigated and no significant neurological or vascular disease was found. Three of the five patients had elevated blood pressure immediately post-treatment,[179] and this has been documented in a separate report, including what was documented as hypertensive crisis in four patients after MAL-PDT. All had known hypertension and were on medication for this.[180] This latter observation is of interest in that blood pressure measurements are not undertaken routinely before, during and after MAL-PDT, but perhaps monitoring of hypertensive patients should be considered. Rarely systemic flu-like symptoms may occur, with a report of intense phototoxic reactions and systemic malaise in two immunosuppressed patients following PDT and this has not previously been reported, so perhaps we need to more actively enquire about this in patients who are severely photodamaged, possibly immunocompromised and receiving PDT to large areas.[122]

1.6 Carcinogenesis

Whilst *in vitro* PDT may have cytotoxic and genotoxic effects,[181,182] the porphyrin-derived molecules used in topical PDT can also have both antioxidant and anti-mutagenic actions.[183] In hairless mouse models, both MAL-PDT and hexylaminolevulinate (HAL)-PDT have separately been shown to delay the time to development of SCC, using repeated treatment regimens,[184-187] although caution is required in extrapolating these data to the human setting and indeed only marginal effects on delayed tumour development were seen with daylight PDT when using HAL.[187] However, in a split-face study involving 25 renal transplant recipients, repeated topical PDT at 6-monthly intervals for 5 years delayed the development of AK, supporting an earlier randomised, within-patient study. In this earlier study involving 81 patients with AK treated with either MAL-PDT or lesion-specific therapy such as cryotherapy, the former significantly reduced

the development of new AK, although the effect was not maintained at longer-term follow-up over 2 years.[188] Whilst PDT does not have the same mechanisms of action as ultraviolet radiation (for example, it does not activate p53, although upregulates p21),[189] it is immunosuppressive.[190,191] The immunosuppressive effects of PDT appear to be reduced by lowering the irradiance of light delivery, and by nicotinamide.[192,193]

Unlike many cancer therapies, topical PDT is often repeated and there is no clear evidence of a cumulative toxic effect. However, there are observations of the development of eruptive keratoacanthomas following PDT,[194-196] which may be in association with the trauma inflicted on the skin by PDT aggravating or provoking the development of keratoacanthoma.[197] There are reports of the development of invasive and sometimes poorly differentiated SCC arising within a few months of PDT treatment.[198-200] There are also isolated reports of melanoma developing at the site of PDT[201,202] and of a microcystic adnexal carcinoma developing at a site of SCC *in situ* treated by PDT several years earlier.[203] However, given that the majority of these patients had pre-existing, extensive field change, with pre-cancerous and cancerous change, as well as a history of skin malignancies, association with PDT itself is very difficult to prove and these may well be coincidental cases. Likewise, the development of SCC arising after PDT for erythroplasia of Queyrat of the penis, as an isolated report,[204] may also have been coincidental. A recent retrospective study assessing cases of invasive SCC arising in areas previously treated by topical MAL-PDT identified 10 SCC in 699 treated patients with no significant histological or immune-histochemical differences compared with SCC lesions developing in non-PDT treated areas. The patients who developed SCC all had multiple AK or SCC *in situ* and hence were pre-disposed to invasive SCC development although an association with multiple (median 5 treatments over 1 year) PDT sessions is highlighted.[205] However, vigilance is required, and reporting is to be encouraged. Whilst longer-term follow-up of patients receiving

PDT is ideal, it is often not practical as patients are often elderly and frail, and due to pressures on outpatient services.

1.7 Safety aspects of topical PDT

Contraindications to PDT include a history of porphyria and allergy/photoallergy to active ingredients of the applied photosensitizer.[143,145,196] Most PDT is carried out using red light which is not phototoxic to the retina. However, blue light can pose a hazard to the retina, potentially causing irreversible damage to the photosensitive neurotransmitters in the macula.[206] Wearing goggles, for both patient and staff, is recommended to limit the transmission of high-intensity light and to avoid discomfort and disturbance of colour perception. Following topical PDT, localized photosensitivity can remain for up to 48 h.[124,207]

1.8 Conclusions

In summary, topical PDT is a widely used and evaluated therapy, which is generally very well tolerated by most patients. Whilst pain and discomfort during irradiation are the main adverse effects during conventional PDT, adjustment of irradiation regimens, including the use of low irradiance options such as dPDT, generally ensures that PDT can be administered effectively and safely. Other expected skin phototoxicity effects, notably erythema and oedema, resolve rapidly over a few days and longer-term adverse effects, such as pigmentary change, scarring or contact allergy, are uncommon. Thus, PDT has an important place in the management options of patients with superficial non-melanoma skin cancer and dysplasia as highlighted in current guidelines.[1]

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Table 1: The adverse effects of topical photodynamic therapy

Adverse effect	Prevalence
Discomfort and/or pain	Common
Erythema, oedema, exudation, crusting (phototoxicity)	Common (expected)
Sterile pustules	Relatively common when treating acne
Urticaria	Uncommon
Infection (bacterial or viral)	Uncommon
Purpura and/or bruising	Uncommon
Scarring (hypertrophic or atrophic)	Uncommon
Milia	Uncommon
Photo-onycholysis	Uncommon
Dyspigmentation (increased or decreased pigmentation)	Uncommon
Changes in hair growth (increase or loss)	Uncommon
Dermatitis and contact allergy to pro-drug	Uncommon
Systemic features: hypertension, flu-like symptoms	Rare and unproven
Neurological symptoms: nerve palsy, transient amnesia	Rare and unproven
Skin cancer risk	No proven risk and may have preventative role