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PRACTICAL PHOTODYNAMIC THERAPY FOR THE CANADIAN DERMATOLOGIST

Introduction

Photodynamic therapy (PDT) is used in dermatology for the treatment of malignant and non-malignant cutaneous diseases. PDT utilizes a photosensitizing agent and visible light in the presence of oxygen to produce reactive oxygen species (ROS). ROS then induce apoptosis of cellular components leading to cell death.[1] PDT is approved in Canada for the treatment of non-hyperkeratotic actinic keratoses (AK)[2,3] and superficial basal cell carcinoma (BCC) outside the H-zone of the face.[2] In addition, some European countries have approved its use in the treatment of squamous cell carcinoma *in-situ* (SCCis) and thin nodular BCC.[4]

Off-label uses of PDT include acne, photoaging, infectious dermatoses, and malignancies such as cutaneous T cell lymphoma (CTCL), and extra-mammary Paget's disease.[5] This review will focus on the practical use of PDT for the treatment of premalignant and malignant lesions.

Mechanism of Action

For dermatologic conditions, PDT is carried out by topical application of precursors of the heme biosynthetic pathway, specifically 5-aminolaevulinic acid (5-ALA) or its ester, methyl aminolaevulinate (MAL). In Canada, there are two photosensitizers approved to treat AK: Levulan®Kerastick (5-ALA) (DUSA Pharmaceuticals Inc.) and Metvix (MAL) (Galderma Canada Inc). Only Metvix is approved for the treatment of superficial BCC in Canada. During an incubation period, these precursors are converted within target cells into protoporphyrin IX (PpIX).[1] PpIX has major absorption peaks in the visible spectrum of light, particularly in the blue (410-420nm) and red (630-635nm) wavelengths **(Figure 1)**. After incubation, visible light in the blue (5-ALA) or red (MAL, 5-ALA) spectrum is used to activate the photosensitizer. Light sources used include narrowband LED devices, metal halide lamps, fluorescent lamps, filtered intense pulsed light (IPL), and lasers.[4]

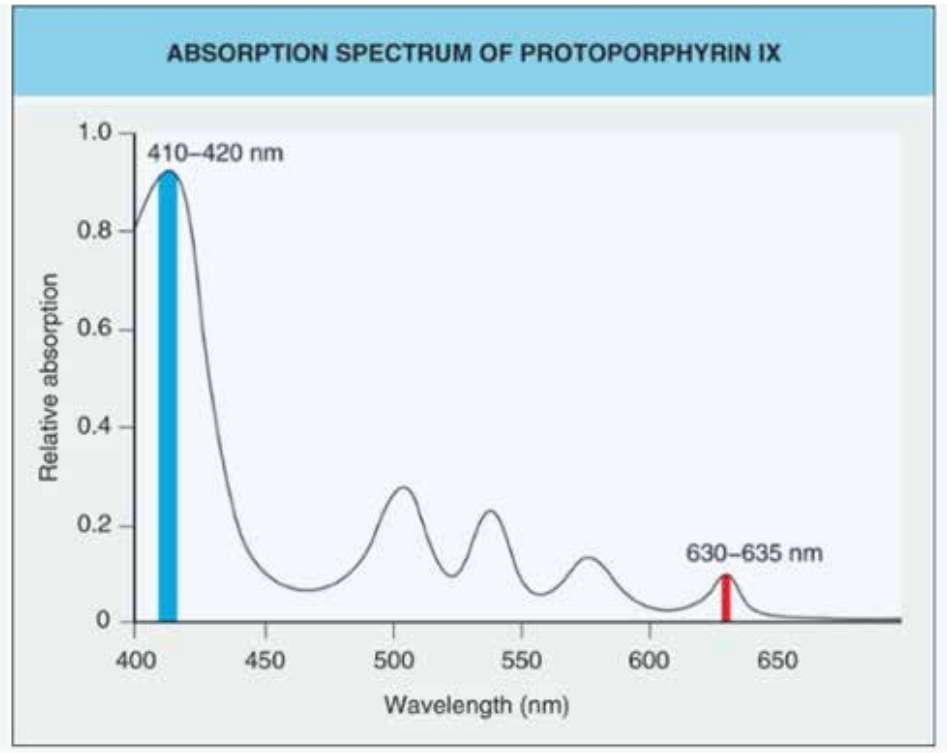

Figure 1: Absorption spectrum of protoporphyrin IX; adapted from Liu and Richer, 2018

When light at the appropriate wavelength is absorbed by PpIX, it excites the PpIX to a higher energy "singlet" state. This singlet state molecule can then transfer its energy to oxygen, producing singlet oxygen and other reactive oxygen species. It can also release energy as photons, which is seen as fluorescence when a Wood's lamp is shined on the treated field.[6] The ROS interact with components of the cell, leading to apoptosis and cellular necrosis. Tumour destruction is kept localized by several factors: preferential accumulation of porphyrins in both malignant and pre-malignant cells, the targeted application of the photosensitizer, limiting the area of light exposure to only the specific skin target, and photobleaching (deactivation) of the photosensitizing chemical with continued light exposure.[7]

Methods of Administration

Patient selection is important prior to performing PDT. Contraindications to PDT include hypersensitivity to the photosensitizing agent (MAL or 5-ALA) or ingredients in the formulation (peanut and almond oil in Metvix), a history of photosensitive disorders, history of porphyria, and morpheaform basal cell carcinoma.[2,3]

Conventional PDT (c-PDT) involves the application of the 5-ALA or MAL photosensitizer followed by occlusion for 3-4 hours, then exposure to the appropriate activating wavelength of light. Protocols for current approved indications are summarized in **Table 1**. For AK, clinical trials have demonstrated a lesion clearance rate of 83-92% at 3 months and a one-year sustained clearance of up to 78-80%.[11,12] In comparative studies, c-PDT was superior to cryotherapy[13], diclofenac[14], and 50% trichloroacetic acid[15] in the clearance of AK. It has comparable clearance rates to topical 5-fluorouracil (5-FU)[16], imiquimod[17], and ingenol mebutate.[18] However, patients rate the cosmetic outcome of PDT higher than other AK treatments, with the exception of imiquimod, which was equivalent.[4,19]

Superficial BCC has a primary clearance rate of 92-97% at 12 weeks using MAL-PDT, with a 1-year recurrence rate of 9% and 5-year recurrence rate of 22%.[20] While some European countries approve the treatment of nodular BCC with c-PDT, the response rates are lower and recurrence rates higher than with superficial BCC. Conventional MAL-PDT is also approved for SCCis in many countries, with lesion clearance rates of 86-93% and a 2-year sustained clearance rate of 68-71%.[21] Nodular BCC and SCCis treatment with PDT is off-label in Canada. PDT is not recommended for other subtypes of BCC or invasive squamous cell carcinoma (SCC).

Daylight PDT

Daylight PDT (d-PDT) involves the application of sunscreen to the entire face, followed by MAL application to the affected areas, and a short 30-minute incubation time. Ambient outdoor light is then used to activate the MAL over a longer period of time (2 hours) than c-PDT.[10] This approach allows for the exposure of large surface areas and minimizes pain. However, d-PDT requires certain environmental criteria to be met in order to be effective. The mean outdoor temperature must be above 10°C, or an insufficient amount of PpIX may be generated. Also, patients need a sufficient light-dose to ensure complete activation of the photosensitizer. At northern latitudes such as Canada this typically restricts d-PDT to the months between April-October.[22,23] D-PDT is approved for the treatment of actinic keratoses, and is as effective as c-PDT, but is much less painful.[24,25] The original Australian and European studies demonstrated 70-89% clearance of AK after treatment. D-PDT is

not approved for the treatment of BCC, SCCis or SCC.

Technique Variations of PDT

There are several techniques used to enhance the efficacy of PDT, though all are considered off-label. Pretreatment of lesions to improve penetration of the photosensitizer can be done chemically with topical keratolytics such as retinoids, salicylic acid, and a-hydroxy acids. Physical modalities such as tape-stripping, fractional CO2 laser[26], and microneedling[27] have also been used. Laser-assisted PDT was found to be significantly more effective than PDT alone, with no difference in pain intensity, especially for clearance of AK on difficult sites such as the extremities.[26]

The use of combination field therapies such as imiquimod, 5-FU, and calcipotriol prior to PDT also increases efficacy, with combination treatment showing higher clearance rates when compared with PDT alone.[28] Pretreatment with topical 5-FU cream, applied twice daily for 6–7 days prior to PDT, led to a mean improvement in lesion clearance of 11–30% compared with PDT alone. Imiquimod, when used either pre-or post-PDT, led to higher rates of complete clearance than PDT monotherapy.[28] However some combined treatment regimens trade increased efficacy for increased pain and local side effects, such as with calcipotriol pretreatment.[29] Elevating skin temperature after ALA/MAL application has also been shown to increase short- and long-term efficacy of AK clearance by up to 90%.[30] This is based on the fact that PpIX creation is a temperature-dependent process, so an increase in PpIX conversion and accumulation may lead to increased clearance of AK.[30] This technique does not lead to increased pain, and has the benefit of shortening incubation time.

Adverse Effects and Complications

PDT is not without adverse effects. First and foremost is photosensitivity. Patients must be aware that they will develop a phototoxic reaction during PDT treatment.[31] This presents as pain, erythema, edema, exudation and crusting. Patients must avoid sunlight for 48 hours after PDT is performed, allowing any residual photosensitizer to be slowly photobleached by indoor visible light. The use of conventional sunscreens is insufficient to protect treated areas after PDT, as residual photosensitizer can be activated by visible light, and most sunscreens do not protect in this wavelength. D-PDT typically generates milder local inflammation that resolves faster than c-PDT. These reactions resolve over 1-3 weeks, and any wounds heal by secondary intention. Scarring is a rare, uncommon side effect, and PDT is being investigated as a treatment option for hypertrophic and keloid scars. As mentioned above, the ultimate cosmetic outcome after PDT is preferred over other field therapies by patients in many studies.[4]

Pain or discomfort is a common adverse effect of c-PDT, and many strategies have been used to mitigate this. There is a large variation in the intensity of PDT-induced pain between patients, but up to 16-20% of patients report experiencing severe pain.[32] Once the treated area is exposed to light, patients experience a range of symptoms from a prickling sensation, to burning, or a "stabbing" sensation. This typically builds with the length of exposure and varies with the rate of light delivery. D-PDT has a lower irradiance of light exposed over a longer period of time, leading to significantly less pain.[24] Effective techniques to mitigate pain include treatment interruption, talking and distraction, fans or cold forced air directed at the site, application of ice packs or cold sprayed water, and anesthesia through local infiltration or nerve blocks.[31] Topical agents such a lidocaine, eutectic mixture of local anesthetics (EMLA), tetracaine, or capsaicin are ineffective at mitigating the pain of PDT.[31] Many guidelines recommend using multiple options for pain mitigation simultaneously. Although pain is frequently reported during PDT treatment, only 2% of PDT treatments are discontinued due to pain.[33]

Lastly, less common adverse reactions to PDT include flaring of latent herpes simplex infections, and open wounds may rarely lead to a secondary bacterial or viral infection. Rarely, urticaria, purpura, alopecia, dyspigmentation or milia may develop to treatment sites. Contact hypersensitivity may develop in patients who have undergone multiple PDT treatments, had large areas treated, or in staff administering the treatment. As such, gloves are recommended for healthcare providers handing MAL and ALA to avoid contact sensitization.[34]

Conclusion

In summary, topical PDT is a widely used therapy which is generally well-tolerated by patients. It offers efficacy similar to other standard treatments, combined with excellent cosmetic results. While pain and discomfort are the main adverse effects of c-PDT, effective strategies have been developed to manage discomfort. This includes the development of d-PDT, which is a relatively pain-free treatment option allowing treatment of larger surface areas with equivalent results. Careful patient selection and thorough counselling, both pre-procedure

	C-PDT with 5-ALA[8]	C-PDT with MAL[9]	D-PDT with MAL[10]
Indication	Single and multiple non-hyperkeratotic actinic keratoses of the face and scalp	1) Thin or non-hyperkeratotic AK on face and scalp. 2) Superficial BCC 3) SCCis (Europe)	Thin or non-hyperkeratotic, non-pigmented AK on face and scalp
Lesion Preparation/ Photosensitizer application	Curettage of hyperkeratotic lesions. Apply solution to AK and let dry. Incubate for 14-18 h overnight. Treatment site not occluded, but protect from sun/bright light. Off-label use: incubate 3h with occlusion[9]	Curettage of hyperkeratotic lesions. Remove scales/crusts, roughen surface. Apply layer of cream ~1 mm thick via spatula to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 h.	Apply mineral sunscreen (SPF 30-50). Once dry, remove scales and crusts, roughen skin. Apply thin layer of Metvix to treatment area. No occlusion
Photosensitizer	ALA 20% hydroalcoholic solution (Levulan Kerastick)	MAL 16.8% cream (Metvix/Metvixia)	MAL 16.8% cream (Metvix/Metvixia)
Light Source	Blue, fluorescent light (417nm wavelength)	Red LED light (630nm wavelength)	Ambient daylight
Illumination Protocol	Rinse and pat dry prior to light exposure. Irradiate treated area for 1000 seconds (16 minutes 40 seconds) to achieve total dose of 10 J/cm^2	Rinse with saline. Irradiate using red light of spectrum 630-635nm to a total dose of 37 J/cm^2	Patient goes outside within 30 min of application. Dry day, temperature >10°C, exposure time of 2 hours
Cream Removal and Aftercare	Avoid sun for 30-48 hours	Wipe clean with saline.	Remove MAL with warm water and washcloth. Avoid sun for 24 hours
Treatment Frequency and Follow up	One treatment. Follow up in 8-12 weeks.	1) AK: one treatment 2) BCC: 2 treatments, 1 week apart 3) SCCis: 2 treatments, 1 week apart	Single treatment. Follow up in 7 days and reassess at 12 weeks.

Table 1: Treatment protocols for approved indications

and post-procedure, are key to the successful delivery of PDT. Topical PDT has an important place in the management of patients with precancerous lesions and superficial nonmelanoma skin cancer, with further research ongoing to increase its efficacy and broaden its successful clinical usage.

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