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A REVIEW OF METVIX FOR THE TREATMENT OF ACTINIC KERATOSES, SUPERFICIAL BASAL CELL CARCINOMA AND FOR USE IN DAYLIGHT PHOTODYNAMIC THERAPY

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Introduction

With increasing sun exposure and an aging population, skin malignancies dysplasia are becoming more prevalent. This includes premalignant actinic keratoses (AK), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and other skin cancers. Many treatment options are available for these conditions, including cryotherapy, surgery, topical field therapy creams, and photodynamic therapy (PDT).

PDT utilizes a photosensitizing agent and visible light in the presence of oxygen to produce reactive oxygen species (ROS), which then induce apoptosis of cellular components leading to cell death.[1] Conventional PDT (c-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] It is also used off label for the treatment of squamous cell carcinoma in-situ (SCCis), which is an approved indication for PDT in many European countries.[4] Daylight PDT (d-PDT) using methyl aminolaevulinate (MAL) for AK is also approved by Health Canada. In Canada, there are two approved topical photosensitizers: Levulan® Kerastick (5-Aminolevulinic acid or 5-ALA) (DUSA Pharmaceuticals Inc) and Metvix (MAL) (Galderma Canada Inc). Only Metvix is approved for the treatment of AK, superficial BCC and for the use in daylight PDT in Canada, and as such it is the focus of this article.

Identification

Both AK and superficial BCC develop in anatomic areas that receive extensive sun exposure, including the face, balding scalp, forearms, and dorsal hands.[5] BCC may also develop on the trunk and lower extremities. AK present as rough scaly papules on an erythematous base that have varying amounts of overlying epidermal hyperkeratosis.[6] They can present as a solitary lesion, multiple AK or as part of field cancerization of a sun exposed site. Clinical diagnosis is typically sufficient, but a biopsy may be required if a clinician is concerned about the possibility of SCCis or SCC.

Superficial BCC present on sun exposed skin as a well-demarcated scaly erythematous patch or plaque, typically located on the trunk and lower extremities. Ulceration can also be present.[7] A biopsy is typically required to confirm the diagnosis, as SCCis and inflammatory dermatoses have a similar clinical appearance.

Patient Selection

Patient selection is important prior to performing PDT. The procedure should be medically appropriate for the patient, and they should be well counselled and aware of the risks, benefits, and alternatives to PDT. Contraindications to PDT include hypersensitivity to the photosensitizing agent or ingredients in the formulation (peanut and almond oil in Metvix), a history of photosensitive disorders, a history of porphyria, and a histologic diagnosis of morpheaform basal cell carcinoma.[2,3] For AK, PDT is more appropriate for treating multiple thin, nonhyperkeratotic AK and field cancerization than solitary AK or hypertrophic AK. Vigorous curettage is required prior to treatment if hyperkeratotic AK are present. When considering using PDT for BCC, the tumour in question should be considered low risk for recurrence. Factors that make a BCC low risk include: location outside of the H zone of the face, size (< 20 mm on the trunk or extremities, < 10 mm on the face), superficial or nodular histologic subtype, lack of perineural invasion, and the patient should not be immunocompromised.[8]

Thorough counselling around the PDT procedure and possible adverse effects is extremely important. This procedure can affect a patient's lifestyle for a few days to weeks. An important side effect of PDT is photosensitivity. Patients must be aware that they will develop a phototoxic reaction during PDT treatment.[9] This presents as discomfort, 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. 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 in fact the cosmetic outcome after PDT is preferred over other field therapies by patients in many studies.[4]

The PDT procedure may cause flaring of latent herpes simplex infections, and open wounds may rarely lead to a secondary bacterial or viral infection. As such, patients with a history of herpes simplex should be pretreated with oral antivirals prior to and following PDT. Including a topical antibiotic ointment in the post-procedure care can lower the risk of secondary bacterial infections. 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.[10]

Lastly, patients should be aware that pain or discomfort during the procedure is a common adverse effect of c-PDT, and there are many strategies that have been used to mitigate these occurrences. 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.[9] D-PDT has a lower irradiance of light exposed over a longer period of time, leading to significantly less discomfort.[11] Although pain is frequently reported during PDT treatment, only 2% of PDT treatments are discontinued due to pain.[9]

Procedure

Photodynamic Therapy Protocol

The mechanism of action of PDT consists of two stages: selective absorption and accumulation of photosensitizer in the target tissue/tumor, and illumination with a specific wavelength of light. The reaction generates ROS that degrade the tumor via apoptosis or necrosis. A detailed description of both c-PDT and d-PDT are presented below and are also presented as an algorithm in **Figure 1**.

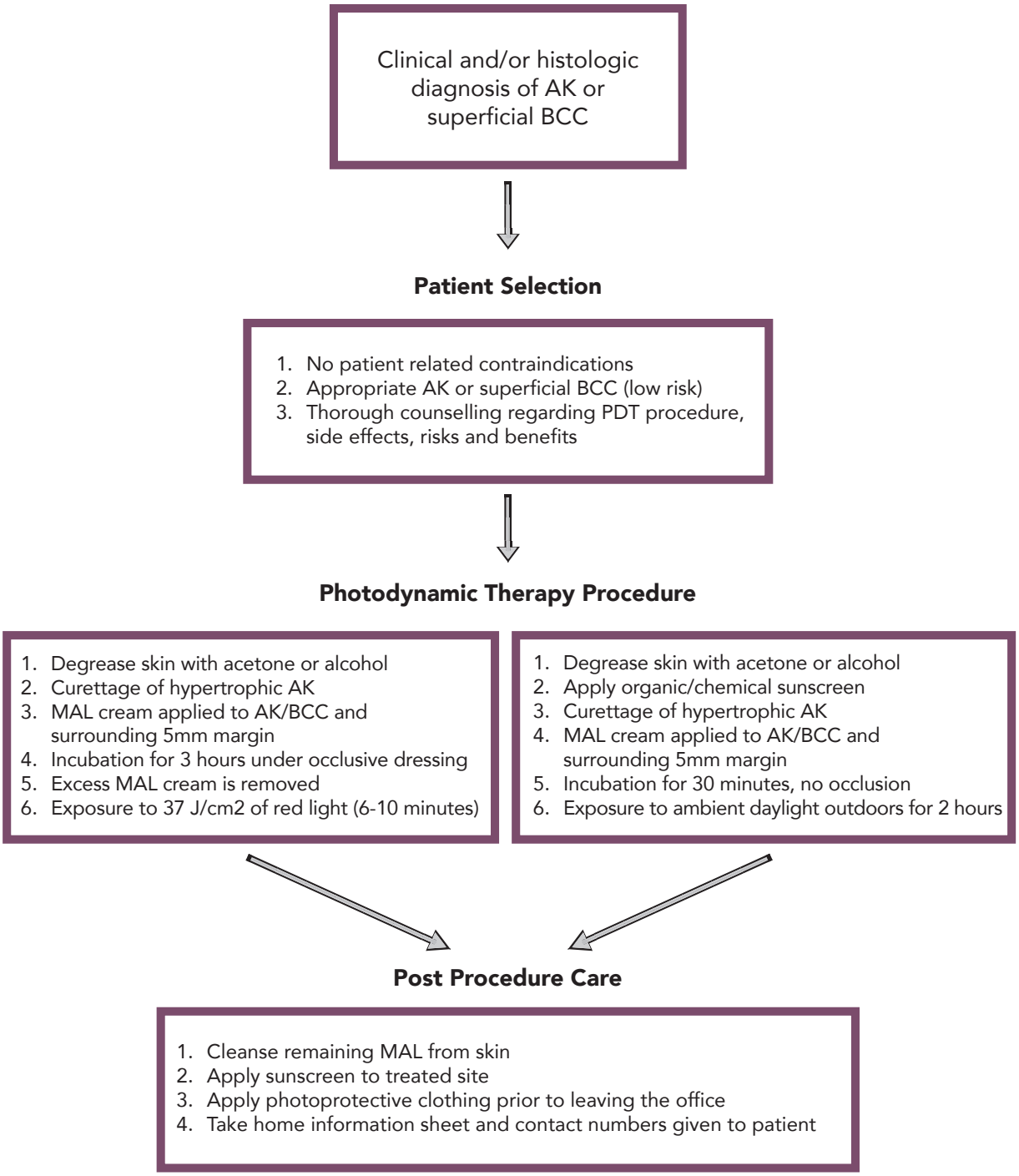

Figure 1: *Conventional and daylight photodynamic therapy protocols; courtesy of Toni Burbidge, MD*

Conventional PDT

Prior to the application of MAL photosensitizer, the patient's skin is degreased with acetone or alcohol and any hypertrophic actinic keratoses are gently curetted. MAL cream is then applied to AKs as well as a surrounding 5 mm margin. An occlusive dressing is applied over the cream, and the MAL is left to incubate for 3 hours. Following the incubation period, the occlusive dressing is removed, and excess MAL cream is wiped from the skin. The treatment site is then positioned under the light source, which in c-PDT is the Aktilite CL 128 lamp (Galderma SA, Lausanne, Switzerland). Other light sources that produce the desired red (630-636 nm) wavelength of light required to activate MAL have been used off-label in studies, but this paper will discuss the conventional protocol only. The Aktilite CL 128 lamp

is positioned 5–8 cm over the area to be treated and irradiation with a total light dose of 37 J/cm^2 is completed, typically taking 6-10 minutes. Any remaining MAL is then cleansed from the skin, and sunscreen is applied to the entirety of the treated site. Sun protective clothing should be worn when leaving the office, such as a hat, scarf, or full sleeves depending on the treated site. If the patient is being treated for a superficial BCC or SCCis, this full PDT treatment is repeated to the site in 1 weeks' time.[12] 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%.[13] Superficial BCC have 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%.[14]

Daylight PDT

Daylight PDT is a protocol allowing for the exposure of large surface areas while minimizing discomfort. However, d-PDT requires certain environmental criteria to be met to be effective. The mean outdoor temperature must be above 10°C, or an insufficient amount of protoporphyrin IX may be generated from MAL. Also, patients need a sufficient light-dose to ensure complete activation of the photosensitizer. At northern latitudes such as in Canada, this typically restricts d-PDT to the months between April and October.[11]

Like the pre-procedure site preparation for c-PDT, the patient's skin is first degreased. A chemical sunscreen is then applied to the entire face to prevent sunburn but allowing visible light to activate the photosensitizer. Any hypertrophic AK are then curetted. Topical MAL is then applied to AK and a surrounding 5 mm margin and left to incubate for 30 minutes without occlusion. The patient is then instructed to go outdoors for 2 hours. After the procedure, any remaining MAL is cleansed from the skin and sunscreen is applied to the entirety of the treated site prior to the patient leaving. Sun protective clothing is also recommended post-procedure for 48 hours.[12] The original Australian and European studies demonstrated 70-89% clearance of AK after treatment, demonstrating that d-PDT is as effective as c-PDT, but has the advantage of less discomfort.[11]

Aftercare and Patient Follow-up

Following the PDT treatment, detailed after care instructions should be reviewed.[15] Patients should be instructed to avoid exposure to the sun for 48 hours to prevent continued activation of the photosensitizer and an exuberant reaction. After 48 hours they should continue to wear sunscreen with an SPF of ≥ 30 for several weeks. To manage discomfort after the procedure, cool wet compresses or a cooling mist spray can be applied at home as needed. Ibuprofen, acetaminophen or aspirin can be taken for discomfort if required, and an antihistamine can be taken if itching or swelling occur. A moisturizer should be applied to the treated area twice daily until any flaking or crusting has resolved and healed. The inclusion of a topical antibiotic either with the moisturizer, or alone, can decrease the incidence of bacterial superinfection.

As the reaction from PDT can differ for everyone, providing a handout or contacting patients by phone following the procedure can help answer questions, reassure patients and lead to better outcomes.

Conclusion

Topical photodynamic therapy (PDT) is widely used to treat superficial nonmelanoma skin cancer and dysplasia. It is equally or more effective than other topical field therapies and achieves cosmetically superior results. Appropriate patient selection, thorough counselling, and supportive aftercare will provide the best experience for patients as well as optimal results, allowing more dermatologists to be comfortable implementing PDT in their practice.

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