Background
Sunlight had been used to treat skin diseases for centuries. As early as 1400 BC, there had been documentations on the use of photodynamic therapy (PDT) in Egypt when people with vitiligo were given certain plant extracts and then exposed to the sun for treatment. In 1911, Hausman described the ability of light-activated hematoporphyrin to photosensitize guinea pigs and mice. In 1913 Meyer-Betz showed that hematoporphyrin could photosensitize humans by injecting himself with hematoporphyrin and noting swelling and pain in parts of his body exposed to sunlight. However, Meyer-Betz also endured skin phototoxicity for 2 months, which was a major drawback in the use of hematoporphyrin as a photosensitizer1.

To overcome the prolonged risk of phototoxicity, Kennedy and colleagues2 introduced topically applied 5-aminolevulinic acid (ALA) in 1990. ALA is a photosensitizing “prodrug” that can penetrate the stratum corneum of abnormal cells and is converted to protoporphyrin IX (PpIX) in the skin. PpIX is subsequently activated by an appropriate light source. Since then, photodynamic therapy (PDT) has been applied to almost every type of cutaneous cancer and numerous skin disorders e.g. actinic keratosis, superficial basal cell carcinoma, Bowen's disease, patch and plaque stage mycosis fungoides, psoriasis, acne vulgaris and photorejuvenation. In the United States, the Food and Drug Administration (FDA) only approved the use of PDT in the treatment of non-hypertrophic actinic keratosis of the face and scalp with delta aminolevulinic acid (Levulan Kerastick®, Dusa Pharmaceuticals, Inc.) after a 14 hour to 18 hour skin contact time and activation with a blue light source (417 nm).

Mechanisms
PDT requires the presence and interaction of three components: photosensitizer, light, and oxygen. ALA must penetrate the stratum corneum of the target area and ALA-induced PpIX must accumulate in sufficient quantity to have a therapeutic effect. Fluorescence studies show that ALA penetration decreases with skin thickness and increases in the presence of photo-damage and other skin abnormalities such as actinic keratosis, psoriasis and basal cell carcinoma. Once inside, ALA diffuses through the epidermis into the dermis but despite that, very little PpIX is actually found in the dermis as demonstrated in fluorescence studies. As a result, ALA PDT can eradicate epidermal cancers without seriously damaging the dermis, thus avoiding scarring2. The time for ALA to diffuse to 3.0 mm from the skin surface has been estimated to be between 3 hours to 15 hours.

When enough PpIX has accumulated, the treatment area is exposed to the wavelengths of light absorbed by PpIX. In general, the longer the wavelength, the deeper its penetration. In PDT, activation of photosensitizer generates products that can destroy cells. The primary cytotoxic agent is believed to be singlet oxygen, a metastable intermediate produced, when photosensitizer is activated. Cell death has been shown to involve an apoptotic mechanism. In the treatment of skin cancer with PDT, vascular injury also plays an important role in tumour destruction as PDT induces changes in both tumour and surrounding microvasculature.

Treatment of Actinic Keratosis
Actinic keratosis is considered by some to be an in situ cancer. Although the natural history of a specific lesion is unpredictable, all actinic keratosis should be treated to avoid progression to squamous cell carcinoma. Different experiments with a variety of light sources including blue light (417 nm), red light (635 nm), pulsed dye laser and intense pulsed light (IPL) had been shown to activate PpIX with ALA incubation times ranging from 3 hours to 24 hours.

In most cases, cure rates for actinic keratosis lesions exceeded 75% with a single treatment. Adverse effects included localized oedema and erythema as well as mild stinging and burning sensation during treatment. The recurrence rate of actinic keratosis lesions treated with ALA PDT had been studied by Fowler and colleagues3 and they reported that four years after treatment, 69% out of 32 lesions in four patients were still clear, 9% recurred, and 22% were “uncertain.” Having established the safety and efficacy of ALA PDT, more research has been done to make the procedure more practical4,5. These studies collectively showed that short-contact (30 minutes) and wide field ALA PDT
provides efficacy and safety in the treatment of non-hypertrophic actinic keratosis. In addition to the treatment of actinic keratosis, improvement on the skin texture of the patients treated with ALA PDT had also been noted by the investigators and they proposed that ALA PDT may be used as a form of non-ablative skin rejuvenation. In another study, PDT with one hour ALA incubation and blue light activation had been shown to clear actinic keratosis as effectively as topical 5-fluorouracil.

In general, the number of treatments depends upon clinical indication and response. Usually, two to five treatments will be given at four week apart. It is important to vary drug incubation time and fluence to achieve desired clinical response. Resolution of actinic keratosis correlates directly with the amount of post-treatment redness and peeling. Although responses vary among patients, the absence of redness for 48 hours after treatment generally indicates that the ALA incubation time was insufficient to achieve the therapeutic level, and that the ALA incubation time should be increased. Alternatively, higher penetration of ALA could also be achieved with a more vigorous skin preparation that removes the keratin layer before incubation, e.g. microdermabrasion and acetone scrub. With more aggressive treatment regime, fewer treatment sessions are required to achieve the same clinical endpoint. Therefore, ALA incubation time may be gradually increased from 30 minutes to 90 minutes, depending on the patient’s tolerance.

PDT is useful in the treatment of actinic keratosis because it can offer field treatment in addition to the treatment of individual lesions. However, it may not work as well on thicker lesions. Common side effects include pain, erythema, crusting, blistering and post-inflammatory hyperpigmentation. The treatment parameters, such as the type and dosage of photosensitizer, light device, fluence, and number of PDT sessions can vary according to the clinical response. In Asian skin, post-inflammatory hyperpigmentation is relatively common and therefore, less aggressive regime is more suitable.

**Suggested Treatment Algorithms**

**Pre-Treatment Care**
1. Continue other topical or systemic medications as required.
2. For patients with thick actinic keratosis, consider treating with a short course of imiquimod or 5-fluorouracil beforehand.

**Treatment Protocol**
1. Wash area to be treated with soap, water and alcohol.
2. Perform single pass microdermabrasion, and scrub area with acetone.
3. Prepare 20% ALA by crushing ampoules and shaking the Kerastick for three minutes.
4. Apply ALA liberally but avoid the mucous membranes.
5. Allow ALA to incubate for at least 30 minutes.
6. Remove ALA with soap and water and wipe with alcohol.
7. Apply appropriate light sources. For example, apply blue light (417 nm) for 15 minutes as a single light source or 5 minutes when used in combination with IPL.

**Post-treatment Care**
1. During the whole course of treatment, apply titanium dioxide or zinc oxide sun-block with a sun-protection factor (SPF) of at least 30.
2. Instruct patient to avoid direct sun exposure for 48 hours immediately after PDT.
3. Tell patient to expect desquamation and sunburn-like reaction with mild to moderate redness and erythema for up to 72 hours.
4. Apply moisturizers liberally.

**Conclusions**

PDT is a safe and effective modality for the treatment of non-hypertrophic actinic keratoses. Since downtime is minimal, the technique is suitable for patients of all ages and lifestyles. Additional cosmetic benefit is also seen but as post-inflammatory hyperpigmentation is a major problem in Asian skin, sun protection is extremely important.

**References**