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Short Review

A Review of Photodynamic Therapy with Enhancement for the Treatment of Actinic Keratosis

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Abstract

Actinic keratosis are the earliest lesions in the continuum of the development of squamous cell carcinomas and, therefore, should be treated. Although they may appear as unique lesions, field canalization is the norm. Various modalities are used periodically throughout a patient's lifetime. In an effort to address better and longer clearances, combination sequential therapies including topical and mechanical treatments either prior or post photodynamic therapy have been tried. Treatment protocols should be tailored to an individual patient at a specific point of time to achieve the best results. There are a few case and anecdotal reports, however, there have not been controlled clinical evaluations. This is a review of possible algorithms that are used, but definitive studies should be done.

Keywords: Actinic keratosis, Photodynamic Therapy, Squamous Cell Carcinomas

Introduction

Actinic keratosis are the earliest stage in the continuum of squamous cell carcinoma, therefore, they should be treated to avoid possible further development. It is estimated that 0.025% actinics/year progress to more invasive cancers (Bowen's, etc.) These epidermal lesions may be reddish-brown, pink, scaly rough, mottled, or crusty patches that are most commonly found in light skinned individuals on the face, arms, chest, and back. Although Actinic keratoses may be single entities, it is more likely that many lesions develop covering a large area. This is field canalization and the entire area should be addressed to eliminate the damaged cells. Field therapy is also provocative and will elucidate areas of damage that are pre-clinical while treating.

Consideration of treatment modality includes type of lesion, flat or hyperkeratotic, number, location, patient age, health, compliance, social circumstances, efficacy, tolerability, convenience, cosmesis, and cost. Multiple therapies may be used in one patient.

Many topical therapies including 5-floururacil and its various formulations that try to decrease the reaction making them more user friendly, imiquimod, and ingenol mebutate are available and have good results; however, these rely on patient application and compliance. Curettage and cryotherapy are in-office procedures that are more appropriate for a few unique lesions. Photodynamic therapy was introduced as an in-office procedure to accommodate compliance and field therapy. No one modality gives perfect results and choice of treatment should be tailored to the individual patient and at a specific point in time. Follow-up and repeat treatment throughout an actinic patient's lifetime is the norm; however, the search for a better regimes that achieve increased and longer clearance ensues [1].Sequential therapy is done with this in mind. Sequential therapy involves using one modality followed by another after a short period of healing to enhance results. Some healing is necessary to avoid undue reactions and to actually attack what actinic lesions that have been left behind. This differs from alternating therapy periodically, as is frequently done, using various modalities during a patient's lifetime since sequential therapy it is a planned procedure in a relative close period of time, one procedure following another.

Photodynamic therapy may be done alone or with prior curettage of hyperkeratotic lesions to enhance penetration of the photosensitizer and the results.

Cryosurgery may also be used. With sequential therapy, there should be sufficient brief healing time after topical therapy before or after the PDT so as not to cause undue reactions.

Photodynamic Therapy (PDT) requires the application of a photosensitzer such as 20% aminolevulinic acid to an area, an incubation period, and exposure to a light source such as blue or red light, laser, or pulsed light. Natural sunlight has been used, however, this does not eliminate exposure to the damaging ultraviolet rays and may send the wrong message to the patient that sunlight is not dangerous. The incubation period can be variable in an effort to decrease strong reactions realizing penetration and reaction may be influenced by the amount of time of incubation. PDT gives good results and is an excellent treatment for field therapy. The 5-ALA that is accumulated in damaged cells is converted by the light to protoporphrin IX and generates cytotoxic free oxygen species that targets mitochondrial and plasma membranes in the dystrophic cells. Some patients respond, but not completely and require close follow-up treatments to achieve better success. This opens the question of using other mechanisms to enhance PDT and the results. Penetration, itself, can be enhanced by incubation time, pre-treatment with microdermabrasion, cryosurgery, curettage, peels, scrubs, or other modalities. There are case reports in the literature, but few controlled clinical studies that evaluate different protocols. The key is to tailor the procedure to the individual.

When challenged after 4 weeks of healing time with 5-fluorouracil cream twice daily for 3 weeks, there was a good erythematous response indicating not all the damaged cells had been eliminated with the PDT regime alone.2 Fluorinated pyrimidine 5-fluorouracil blocks methylation of deoxyruidilic acid to thymidyllic acie altering only fast dividing cancerous cells [2].

PDT has been used followed by a course of imiquimod 5% cream and healing time of a few weeks. Imiquimod regulates encoded cytokine levels like alpha-interferon, TNF, and interleukin 12 in mRNA to modify immune responses. The direct pro-apoptotic effect in damaged cells is a result of bypassing transduction paths activating caspase-3 downstream of membrane-bound death receptors. It is a toll-like receptor agonist acting on endosomal membrances. The sequential use of these two modalities increases response and longevity of results [3].

Ingenol mebutate 0.015% has been used as a pre-treatment prior to methyl aminoleuvulinate photodynamic therapy (MAL PDT) in an effort to evoke better results. It can also be used post PDT to achieve better results in the patient. It augments neutrophil-killing ability of abnormal cells by damaging mitochondria. It also has an antiangiogenic property that promotes healing when used after a therapy [4].

Photodynamic Therapy is a fast, in-office procedure that sometimes requires enhancement to achieve greater more long-lasting results. It is important to allow a healing period before or after treatment to avoid undesired effects. More definitive studies should be done to give a clear picture of how beneficial this is; however, it is clear that these efforts make sense and is being done frequently and modalities should be tailored to the individual patient.

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