THERAPEUTIC UPDATE

Therapeutic Update on Actinic Keratosis

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Actinic keratosis (AK) is a premalignant skin condition typically seen almost exclusively in Caucasians, due to their fair skin. AKs develop on chronically sun-exposed areas such as the face, the dorsum of the hands and forearms, upper chest, and the scalp of bald men. While AKs have been described as "precancers," histologic and molecular features suggest that they exist in a continuum with invasive squamous cell carcinoma. A small percentage of AKs eventually evolve into invasive squamous cell carcinoma; it is for this reason that eradication of lesions is warranted. The estimated frequency of conversion is from 0.1% to as high as 16%,[1] but the likelihood of a particular AK progressing to invasive squamous cell carcinoma with metastatic potential is impossible to predict.

There are many treatment options that have similar efficacy. Destructive therapies such as cryosurgery or electrodessication and curettage are directed at specific clinical lesions. Medical therapies, also known as field-directed therapies, use a pharmacologic approach to destroy both the clinical AKs and the subclinical lesions in the surrounding skin.

When selecting a treatment, the dermatologist must keep in mind that the expectations of "baby boomers" may be different from patients of prior generations. Patients today desire eradication of lesions with rapid wound healing and minimal cosmetic alteration.[2]

Local destructive therapies are most commonly used when treating a small number of lesions. Field-directed medical therapy is warranted when there are many AKs and extensive photodamage. It has been shown that the combination of targeted destructive therapy with field-directed therapy has a synergistic effect.

I. Local Destructive Therapies

1. Cryosurgery

Cryosurgery is the most popular first-line treatment for AK. Liquid nitrogen, at a temperature of -196°, freezes the lesions and the atypical cells are destroyed. Since melanocytes in the skin are also sensitive to cold, cryosurgery can leave macules of hypopigmentation.

2. Curettage and Electrodessication

The use of curettage and electrodessication is a surgical technique involving the use of a curette to physically scrape atypical cells and electrocautery to obtain hemostasis and thermally destroy additional atypical cells. The technique is most useful for spot treating lesions, especially those that are hypertrophic.

II. Field-Directed Medical Therapies

There are currently 5 topical medications commonly used for the treatment of AKs:

1. 5-fluorouracil (5FU) – (Efudex®, Flouroplex,® and Carac®)

5FU is an antimetabolite drug used in chemotherapy for treatment of colorectal cancer.[3] It is taken up by cells as if it were uracil. Its active metabolites are subsequently incorporated into DNA and RNA, disrupting replication, and causing cell destruction. Common side effects include erythema, crusting and burning. Formulations include a 5% cream or solution, a 2% solution, a 1% cream or solution, and a micronized 0.5% cream.

2. Imiquimod – (Aldara®, Zyclara™)

Imiquimod is an immunomodulator that has been shown to stimulate immune function by inducing cytokine expression, interferon-α (IFN-α),[4] interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Formulations include 5% cream (Aldara®), 3.75% cream (Zyclara®), and 3.75% solution.

3. Diclofenac gel – (Solaraze™)

Diclofenac sodium 3% gel is a nonsteroidal anti-inflammatory drug (NSAID). It is a non-selective cyclooxygenase (COX) inhibitor which also exhibits anti-tumor effects, given that COX-2 has been implicated in keratinocyte proliferation.[5,6] Diclofenac has also been shown to induce apoptosis via death receptor signaling.[7] A lengthy, 3-month treatment course is typically required to eradicate AKs.

4. Ingenol mebutate gel – (Picato®)

Ingenol mebutate is a naturally occurring active substance found in the sap of the plant, Euphorbia peplus.[8] The quick action is thought to arise from both direct cytotoxicity leading to cell death and activation of a neutrophil-mediated inflammatory response.[9] The short duration of therapy is a plus, but the brisk inflammatory reaction can be a drawback. This agent is typically used for only 3 consecutive days (0.015%) for face and scalp, and 2 consecutive days (0.05%) for the trunk and extremities.

5. Photodynamic Therapy (PDT) with 5-aminolevulinic acid (ALA) – (Levulan®, Kerastick®) or methyl-aminolevulinate (MAL) – Metvix®
PDT uses a combination of a topical photosensitizer such as ALA or MAL and a visible light source, such as a blue or red light-emitting diode, pulsed dye laser, or intense pulsed light. Upon exposure to visible light, the photosensitizer is converted to protoporphyrin IX, which generates reactive oxygen species and ultimately induces apoptosis and necrosis.[10,11] Use of PDT is limited to superficial lesions and less effective in hypertrophic AK.[12]

Conclusion

5.2 million office visits in the US each year can be attributed to AKs.[13] Eradication of these common lesions will lower the incidences of invasive squamous cell carcinoma. Regimens that combine targeted destructive therapy with field-directed medical therapy to treat and prevent these premalignant lesions yield the most success. Future research will focus on finding agents with increased efficacy and fewer side effects and downtime.

Disclosure

Dr. Sarnoff has no relevant conflicts of interest to disclose.

References

1. Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol.* 2000;42(1 Pt 2):23-24.
2. Spencer JM, Hazan C, Hsuing SH, Robins P. Therapeutic decision making in the therapy of actinic keratoses. *J Drugs Dermatol* 2005;4:296-301.
3. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer.* 2003;3(5):330-338.
4. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. *J Am Acad Dermatol.* 2000;43(1 Pt 2):S6-11.
5. Maltusch A, Röwert-Huber J, Matthies C et al. Modes of action of diclofenac 3%/hyaluronic acid 2.5% in the treatment of actinic keratosis. *J Deutschen Dermatologischen Gasellschaft.* 2011;9(12):1011-1017.
6. Tripp CS, Blomme EA, Chinn KS et al. Epidermal COX-2 induction following ultraviolet irradiation: suggested mechanism for the role of COX-2 inhibition in photoprotection. *J Invest Dermatol.* 2003;121(4):853-861.
7. Fecker LF, Stockfleth E, Braun FK et al. Enhanced death ligand-induced apoptosis in cutaneous SCC cells by treatment with diclofenac/hyaluronic acid correlates with downregulation of c-FLIP. *J Invest Dermatol.* 2010;130(8):2098-2109.
8. Green AC, Beardmore GL. Home treatment of skin cancer and solar keratoses. *Australas J Dermatol.* 1988;29(3):127-130.
9. Rosen RH, Gupta AK, Tyring SK. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: rapid lesion necrosis followed by lesion-specific immune response. *J Am Acad Dermatol.* 2012;66(3):486-493.
10. Miller IM, Nielsen JS, Lophaven S, Jemec GB. Factors related to pain during routine photodynamic therapy: a descriptive study of 301 patients. *J Eur Acad Dermatol Venereol.* 2011;25(11):1275-1281.
11. Nakaseko H, Kobayashi M, Akita Y et al. Histological changes and involvement of apoptosis after photodynamic therapy for actinic keratoses.*Br J Dermatol.* 2003;148(1):122-127.
12. Wiegell SR, Fabricius S, Gniadecka M et al. Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. *Br J Dermatol.* 2012;166(6):1327-1332.
13. Warino L, Tusa M, Camacho F, et al. Frequency and cost of actinic keratosis treatment. *Dermatol Surg.* 2006;32(8):1045-1049.

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