Actinic keratosis (AK) treatment represents a large and ever-increasing burden to our health care system, with the direct cost of therapy estimated to be more than $1 billion annually. There has been great investment in developing an ideal treatment of AK that is effective, convenient, and minimizes adverse effects. However, differences in lesion distribution, number, and thickness, as well as patient preferences regarding convenience, cost, and tolerance of side effects, weigh heavily on treatment choice and necessitate multiple treatment options.

Although targeting individual lesions with cryotherapy remains the mainstay of many practices, field therapy treats subclinical lesions as well as clinically apparent AK. Indeed, AK is a chronic condition, as field cancerization secondary to cumulative UV light exposure produces new lesions, even following effective therapy. Thus treatment of subclinical lesions that have undergone molecular transformation leads predictably to greater sustained clearance of a treatment field. Furthermore, because several field therapies are patient administered, they allow for decreased reliance on physician visits for administration of therapy.

Topical treatment with 5-fluorouracil (5-FU) 5% is the gold standard of efficacy, demonstrating clinical clearance of 96% following 4 weeks of twice-daily use. However, high rates of adverse effects and extended treatment duration produce decreased adherence and clearance rates in clinical practice, which have led to the development of less concentrated formulations of 5-FU as well as new pharmacotherapies. Diclofenac gel 3% has improved tolerability, though its efficacy is lower than 5-FU. Imiquimod has shown higher sustained efficacy, with newer formulations promising shorter treatment duration. Despite these new therapies, both patients and physicians often opt for the simplicity of more frequent patient visits and treatment with cryotherapy.

Ingenol mebutate (IM) gel, approved by the US Food and Drug Administration in January 2012, offers patients a 2-day therapy for the trunk and extremities (0.05% concentration) and a 3-day treatment of the scalp and face (0.015% concentration). This short duration of treatment results from IM's sustained effect of neutrophil-mediated antibody-dependent cytotoxicity following initial tissue necrosis. Randomized controlled trials have shown efficacy compared to vehicle-controlled trials for both formulations (0.015% and 0.05%), and although local skin reactions are expected with use of IM, they typically resolve shortly after cessation of therapy. Thus IM provides field clearance similar to other therapies but with short duration and good adherence.

Photodynamic therapy (PDT), a physician-administered field therapy, utilizes a topical photosensitizer (e.g., aminolevulinic acid) to produce reactive oxygen species that cause selective destruction of abnormal cells. Although treatment with PDT previously utilized extended incubation times, recent studies have shown efficacy with 1-, 2-, and 3-hour incubation periods, allowing for more convenient therapy. Critically, PDT has a relatively favorable cosmetic outcome. Additionally, PDT, which minimizes therapy burden while maintaining treatment efficacy, may play a powerful role in decreasing the progression of AK to squamous cell carcinoma in organ transplant recipients.

Combination and/or sequential therapy generally is underutilized in the treatment of AK. Field therapies such as imiquimod, IM, and PDT have been used in combination with lesion-directed treatments such as cryotherapy and curettage with improved efficacy compared to lesion-directed therapy alone. Most studies that have evaluated combination or sequential therapy consisting of cryotherapy followed by a topical agent have shown a higher clearance rate of lesions with both therapies versus cryosurgery alone. Although combination therapy may increase initial costs and treatment burden, the potential for greater
sustained efficacy may reduce patient visits and ultimately decrease the burden of therapy.

It may be argued that widely utilized treatments such as cryotherapy are sufficient in most patients with AK if used appropriately and with adequate follow-up. However, with an aging population, a greater demand for health care at large, and an ever-increasing incidence of squamous cell carcinoma, finding optimal therapies that improve efficacy and decrease treatment burden for both patients and health care at large is critical. Although the cost of AK treatment has been evaluated, there are challenges in accounting not only for the changing landscape of drug costs and reimbursement but also the added burden of repeat treatment or further physician visits resulting from therapies with lower sustained efficacy or adherence. Certainly, newer therapies require a period of transition allowing for improved physician familiarity and patient education. To better account for the role played by adherence in efficacy, both compliance and direct comparator studies can better inform physicians on the appropriateness of therapies for particular patients.

REFERENCES

Quick Poll Question
Which topical therapy do you use most often in patients with actinic keratosis?

- a. aminolevulinic acid plus photodynamic therapy
- b. 5-fluorouracil
- c. imiquimod
- d. ingenol mebutate

Go to www.cutis.com to answer our Quick Poll Question and see how your peers have responded.