Topical fluorouracil (5-FU) is a mainstay of treatment for multiple actinic keratoses (AKs). While cryosurgery remains a popular and effective treatment for discreet lesions and photodynamic therapy continues to gain prominence, the use of field-directed 5-FU has grown either as monotherapy for diffuse AK lesions or following other interventions to address subclinical lesions.

The short-term efficacy of topical fluorouracil for AKs is well established across multiple studies. New research suggests that 5-FU offers long-term efficacy, reducing the need for retreatments by up to two years.

Ahead is a look at that study as well as some other recent investigations of 5-FU.

**LONG-TERM EFFICACY OF 5-FU**

Findings on the long-term efficacy of 5-FU come from the Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) trial, which was a randomized, double-blinded, placebo-controlled trial. A total of 932 veterans enrolled. Subjects had had two or more keratinocyte carcinomas in the five years prior to study enrollment.

Subjects were randomized to apply either topical fluorouracil cream, 5% (n = 468) or vehicle control cream (n = 464) to the face and ears twice daily for up to four weeks. Subjects in each group had similar numbers of AKs on the face and ears at enrollment. The mean follow-up duration was 2.6 years in both treatment and control groups.

Investigators recorded for each subject the number of spot treatments for AKs on the face and ears at semiannual study visits and in between study visits. The fluorouracil group had fewer AKs, compared with the control group at six months (3.0 vs 8.1) and for the overall study duration. Complete AK clearance rates were 38 percent for the fluorouracil group at six months, compared to 17 percent for controls. Active treatment subjects had fewer spot treatments at six-month intervals, at study visits, and in between study visits during the trial. The time to first spot-treatment was longer in the fluorouracil group (6.2 months), compared with the control group (6.0 months).

**5-FU PLUS PDT**

Researchers have also turned their attention recently to the use of 5-FU in combination with photodynamic therapy. In an investigator-blinded randomized study of 30 subjects, results suggested that the combined use of 5-FU with ALA-PDT provided better clearance of preclinical AK lesions, compared to 5-FU or PDT alone.

Subject were randomized 1:1:1 into three groups: Pretreatment with 5-FU for six to seven days followed by...
A NOTE ON COSMESIS

Despite the short-term predictable side effects associated with the inflammatory response to topical 5-FU, treatment with the topical agent has been associated with overall improvement in skin, once healed.

In light of these findings, researchers recently compared the efficacy and safety of 5-FU cream 5% to that of peels for photodamaged forearms.

The interventional, randomized, comparative, evaluator-blind study included 32 patients with severe photaging of forearms. Subjects applied 5-FU cream every day for four weeks on one forearm and had weekly peels on the other.

Clinical and histologic findings confirmed the benefits of topical 5% 5-FU. Subjects had improved skin appearance and decreased dermal elastotic material. Immunohistochemistry showed reduced levels of epidermal p53 and increase in the level of procollagen I. And the results were maintained up to and beyond six months.


A NOVEL 5-FU/SA COMBINATION

A formulation containing the combination of 5-FU, 0.05% and salicylic acid, 10% is showing promising efficacy in studies. The formulation, not approved in the US, is approved for management of individual lesions but not field treatment outside the US.

A recent case series followed eight patients with primarily recurrent, multiple AKs who received up to six weeks of field-directed 5-FU/SA. Noninvasive in vivo reflectance confocal microscopy (RMC) was used to monitor the efficacy of topical therapy. Most patients were shown to have complete clearance of clinical/subclinical AKs on various body areas.

SHORT-COURSE 5-FU PLUS CRYOTHERAPY

While field-directed 5-FU is already widely used in conjunction with lesion-directed cryosurgery, a recent study investigated the relative benefits of a shortened course of 5-FU after cryosurgery. Sixty subjects with AK lesions underwent cryosurgery and were then randomized to apply 5-FU cream 0.5% or comparator cream once daily to the study area for 1 week.

Assessments were completed at weeks 3, 4, 8, and 26. After eight weeks, treatment with combination treatment was more likely to result in complete clearance versus cryosurgery alone. At 26 weeks, however, there was no statistical difference in the complete clearance of AK lesions in the combination group compared to cryosurgery alone at 26 weeks. Side effects in the combination group were decreased. This study demonstrated the benefit of combination treatment of cryosurgery with one week of 5-FU compared to cryosurgery alone in clearing AK lesions for two months.

The study authors maintain that larger studies are warranted that may demonstrate a more dramatic benefit for combination therapy compared to cryosurgery alone.

5-FU RE-visited

Recent studies confirm the role of topical 5-FU in the management of actinic keratoses. While the widespread use of combinations of lesion-directed and field-directed therapies is still relatively new, data confirm the safety and efficacy of these approaches. Coupled with new findings about reductions in long-term recurrence rates associated with 5-FU, the data suggest that topical fluorouracil will continue to be a mainstay of treatment for many patients with AKs.

5FU regimens tend to vary from clinician to clinician as there is no one defined way of using this topical chemotherapeutic agent. Most patients have difficulty treating for more than 21 straight days and extensive sun damage can lead to extensive inflammatory reactions. Consideration of “drug holidays” during individual regimens may be in order: treating for five days and then taking two days off for three cycles for example may be tolerate better and lead to improved compliance. No matter the regimen, recent data certainly is suggesting that combination modalities may lead to improved outcomes.

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