Inflammation and irritation are common, troublesome sequelae of topical 5-fluorouracil (5FU) treatment for actinic keratoses. While data have suggested that topical fluorouracil 0.5% may be better tolerated by some patients than the 5% concentration, both are associated with irritation. Nonetheless, 5FU is an effective and often convenient intervention, particularly for patients with multiple lesions. In fact, a relatively recent study concluded that topical fluorouracil 5% remains the gold standard of topical AK therapy.

In order to improve the tolerability of topical 5FU therapy and accelerate healing after treatment, dermatologists have employed topical antibiotic ointments, topical steroids, and various occlusive moisturizers. A novel occlusive wound healing agent may provide particular benefits for reducing irritation associated with topical 5FU therapy.

**Standard Adjuncts**

Although an early study showed that concomitant application of 0.1% triamcinolone cream failed to reduce the irritation associated with topical 5FU 5% therapy, researchers determined that the topical corticosteroid did not interfere with the therapeutic effect of 5FU. Given these findings, many dermatologists prescribe topical corticosteroids for patients who have a robust inflammatory response to 5FU, even if the benefits may be minimal.

Support for concomitant use of topical antibiotic ointments is thin; no studies of their use in this setting have been published, though they have been used historically to dress wounds. These agents may provide some anti-inflammatory effect and may help prevent superficial infections of inflamed skin. That most ointment formulations provide moisturizing effects is an added benefit. Increasing rates of allergic contact reactions to neomycin have led to decreased use of topical antibacterial ointments.

Standard moisturizing agents are also popular for use to help heal and protect the skin throughout the course of topical 5FU therapy. Given its inert nature and lack of associated contact irritant reactions, petrolatum is a standard choice. Occlusive moisturizers represent an exciting area in dermatologic product development. Whereas humectants promote water retention, occlusives lay on the skin and help to prevent transepidermal water loss (TEWL). Combination humectant/occlusive topical formulations have been developed that can protect wound sites in a manner similar to traditional fabric-based occlusive dressings.

Trolamine topical emulsion (Biafine Topical Emulsion, OrthoNeutrogena) is an occlusive hydrating agent formulated to support wound healing. It is indicated for use on wounds, minor abrasions, dermal ulcers, donor sites, first and second degree burns, including sunburns, and radiation dermatitis. It has been used in France for management of radiation dermatitis for several years. Its package insert states that, when properly applied to a wound, the agent “provides an optimum moist environment for the healing process and isolates the wound from harmful germs and other external contamination.” Given these indications and clinical trials data showing that Biafine promotes wound healing, we have adopted it for use during topical 5FU therapy in our practice. To determine whether further investigation of this approach is justified, we compared the healing process among fluorouracil-treated AK patients using Biafine to those of fluorouracil-treated AK patients using white petrolatum.

**Our Investigation**

An eight-week, single-center, investigator-blinded, randomized, parallel designed pilot study randomized 23 patients to one of four treatment groups (Table 1): 5.0% topical 5FU plus Biafine Topical Emulsion (n=6); 5.0% topical 5FU plus white petrolatum USP (n=6); 0.5% topical 5FU plus Biafine (n=5); 0.5% topical 5FU plus white petrolatum USP (n=6). Patients were assessed at...
baseline and at four follow-up visits at weeks 2, 4, 6, and 8. Patients received a two-week supply of study medication at baseline and at weeks 2, 4, and 6 with instructions (Table 2) to apply the agent BID (each morning and evening) to the treatment areas for eight weeks.

The investigator assessed the level of healing of the treatment area(s) according to the scale provided in Table 3.

Findings
A total of 23 patients enrolled in the study. Twenty-one patients completed the study; one subject in each control arm withdrew. The mean age of enrolled subjects was 66.55 years, with a range of 48 to 83 years. All patients were Caucasian.

At week 2, 36.4 percent of Biafine-treated patients were completely healed or almost healed versus 25 percent of patients treated with white petrolatum. Marked healing was evident at week 2 in 54.5 percent of Biafine-treated patients compared to 41.7 percent of those using petrolatum. By week 4, 40 percent of patients using Biafine were completely healed, compared to one third of subjects using petrolatum.

Interestingly in this study, 0.5% topical fluorouracil was more irritating than 5.0% topical fluorouracil. Sub-analysis of patients treated with 0.5% topical fluorouracil revealed that 40 percent of those using Biafine were completely healed or almost healed at week 2, compared to no patients in the white petrolatum group. At week 4, while 40 percent of Biafine-treated patients were completely healed, just 16.7 percent of those in the petrolatum group were...

### Adjunctive Skincare for 5FU-treated Patients
1. Gently wash entire face with an appropriate cleanser and water. Soap-free, moisturizing cleansers are preferred.
2. Avoid loofas or items that mechanically debride the skin. Use of fingertips to apply cleaner is ideal.
3. Pat face dry with a soft towel.
4. Wait about five minutes for the skin to dry entirely.
5. In the morning, apply topical sunscreen, if directed by your dermatologist.
6. Next, apply appropriate adjunctive agents (petrolatum, Biafine, topical corticosteroid) as directed by the dermatologist.
7. Contact your physician if significant erythema, oozing, crusting, or other symptoms develop. If any sign of infection develops, contact the office immediately.

- Avoid use of topical antibiotic ointments except for acutely infected wounds.
Responses to questionnaires from all study subjects showed the sole parameter in which there was a difference in assessments between the Biafine and the white petrolatum groups was reduction in irritation. Biafine-treated patients reported an average reduction of two points, while those using white petrolatum reported an average reduction of 0.5 points.

Adverse events were rare overall and occurred with similar frequency in each arm. Only one adverse event was deemed to be related to study treatment: Mild pruritus of the face with a duration of seven days was attributed to study therapy but resolved on its own without withdrawal of therapy.

**Implications for Care**

Findings from this small pilot study suggest the topical application of Biafine Topical Emulsion by patients undergoing topical fluorouracil therapy is safe and well-tolerated. The topical dressing appears to improve symptoms, such as erythema, inflammation, erosion, and swelling that are associated with topical 5FU therapy. The treatment appears to be at least as effective as topical petrolatum, though it may have particular characteristics (more elegant base, “non-greasy” formulation) that may appeal to patients, but which were not assessed in this trial. Further study to investigate its utility in this setting is warranted. Meanwhile, these findings plus clinical observations to this point suggest that interested patients may use Biafine in conjunction with topical 5FU therapy for AKs.

In an era of escalating antibiotic resistance and increased allergy to antibiotic ointments, the use of topical antibiotic ointments should be limited only to acutely infected wounds; antibiotic ointments should not be used for regular post-surgical wound management in place of occlusive wound care.

It’s worth noting that, while the findings are only observational (the study was not powered to investigate these trends), patients in the fluorouracil 0.5% arms had higher rates of erythema, erosion, crusting, inflammation, and necrosis compared to those in the 5.0% arm. These trends serve as a reminder to clinicians to discuss the risk for adverse events and adjunctive skincare options with all 5FU-treated patients.

**Dr. Kircik has served as an investigator, consultant, or speaker for Ortho-Neutrogena, Dermik, and Valeant.**