



A SUPPLEMENT TO

Skin & Allergy News®



Clinical Dialogues: Actinic Keratosis and Other Nonmelanoma Skin Cancers

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HIGHLIGHTS OF A CLINICAL ROUNDTABLE

Skin Cancer

Topical Agents

Mechanisms of Topical Action

Managing Inflammation

Cheilitis

Cryotherapy

Photodynamic Therapy

Immunocompromised Patients

Bowen's Disease

**Superficial Multifocal
Basal Cell Carcinoma**

Cost Considerations

**Advances In The Treatment
of Verruca Vulgaris**

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The roundtable discussion from which this supplement was developed took place in Washington, DC on February 7, 2004.

This educational supplement to SKIN & ALLERGY NEWS was supported by an unrestricted educational grant from



It was produced by the medical education department of International Medical News Group. Neither the Editor of SKIN & ALLERGY NEWS, the Editorial Advisory Board, nor the reporting staff reviewed or contributed to its content. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or the Publisher.

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CME RECOGNITION

The SKIN & ALLERGY NEWS supplement, "Clinical Dialogues: Actinic Keratosis and Other Nonmelanoma Skin Cancers" is recognized by the American Academy of Dermatology for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

Term of Approval: June 2004-May 2005.

This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.

TARGET AUDIENCE

This activity is developed for dermatologists and other health care professionals involved in the diagnosis, treatment, and long-term management of patients with actinic keratosis (AK), basal cell carcinoma (BCC), squamous cell carcinoma (SCC) in situ, and verruca vulgaris.

EDUCATIONAL NEEDS

AKs, formed by proliferation of neoplastic keratinocytes, are considered by many in the field of dermatology to represent SCC in situ and are treated because of their potential to progress to invasive or metastatic SCC. The risk for metastasis is particularly strong in immunocompromised patients. There have been recent developments in the treatment of AKs. At least one new topical drug has received approval for AK treatment. That topical preparation, like those on the market, must be used with finesse to avoid adverse reactions. Similarly, whereas some of the destructive therapies used for AKs have been around for decades, others are more recent. Dermatologists need information on the variety of ways these topical and destructive treatments can be used, either alone or in combination, in order to accomplish successful long-term eradication of AKs, BCCs, and SCCs.

Verruca vulgaris, or warts, occur commonly on the face, hands, and feet of adults and children. The viruses that cause these warts have little if any malignant potential. However, the American Academy of Dermatology has issued guidelines for their removal, which reflect patient wishes, fear of the warts' spreading, disfigurement, and symptoms such as pain and itching. Pain issues make treatment of warts in children with cryotherapy or laser more difficult than it is in adults. Dermatologists need information on the relatively painless topical treatments that are available to use for wart removal in children.

LEARNING OBJECTIVES

By reading and studying this supplement, participants should be able to:

- Summarize the modalities currently available for the treatment of AKs, and list the major advantages and disadvantages of each.
- Discuss the balance between treatment efficacy and duration of topical therapy as well as the trade-offs between patient compliance and treatment tolerability.
- Describe the risk for metastatic SCC in patients with actinic cheilitis or who are immunocompromised.
- Describe the issues that guide the choice of therapy for treatment of warts in children and discuss which therapies are preferred for treating this age group.

FACULTY AND UNAPPROVED USE DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr Cunningham is a consultant to Valeant Pharmaceuticals International. She discusses the unlabeled use of imiquimod, squaric acid dibutylesterate, cantharidin, cimetidine, DPCD, and candida vaccine for the treatment of warts in children. **Dr Jeffes** is a consultant to Amgen Inc., and Valeant. **Dr Skidmore** discusses the unlabeled use of 5%-fluorouracil, and imiquimod for the use of pre-malignant and malignant cutaneous lesions. **Dr Tanghetti** has received funding from Valeant, and is a consultant to Allergan, Inc., and Valeant. He discusses the unlabeled use of 5%-fluorouracil for Bowen's disease and warts. **Dr Torres** has received funding from 3M Pharmaceuticals, and Lucid, Inc. He is a consultant to 3M, and Valeant. He discusses the unlabeled use of imiquimod for actinic keratoses, and basal cell carcinoma. He also discusses the unlabeled use of 5%-fluorouracil for squamous cell carcinoma. **Dr Werscher** has received funding from Valeant. **Dr Katz** has nothing to disclose.

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Clinical Dialogues: Actinic Keratosis and Other Nonmelanoma Skin Cancers

Actinic keratosis (AK) is the most common premalignant skin tumor, affecting more than 10 million Americans.¹ It is due principally to long-term sun exposure and are experienced by 60% of predisposed individuals more than 40 years of age.² Without treatment, AK lesions may invade the dermis as squamous cell carcinoma (SCC). To maximize successful outcomes, treatment needs to be sensible and economical. Treatment plans must be customized, taking into account aesthetic and practical concerns of daily activities. Fortunately, today's treatment choices outnumber those of the near past, yet skin irritation remains problematic. The experts gathered at this roundtable offer suggestions for optimized management.

—Emil A. Tanghetti, MD

Skin Cancer

DR JEFFES: Although the literature refers to AK as *precancerous*, its histopathology differs very little from that of more advanced SCC, the second-leading cause of skin cancer deaths in the United States. In fact, at least 40% of all cases of SCC begin as AK.¹ Treating AK, therefore, treats the earliest stage of SCC in situ.

DR TORRES: Dermatology needs to undergo a paradigm shift in how it defines and assesses AK. Not only does AK share histopathologic features with SCC, but often they both exhibit the same p53 gene mutation.³ Dermatology should consider the term *keratinocytic intraepithelial neoplasia* to describe AK just as *cervical intraepithelial neoplasia* is used to describe the earliest stage of cervical cancer. Whatever the terminology, treatment is urgent. When a topical therapy clears large areas of noninvasive lesions, detection and treatment of squamous cell lesions become much easier. Furthermore, some topical

AK therapies, such as 5-fluorouracil (5-FU) and imiquimod, very effectively reduce the size of squamous cell lesions, thus assisting subsequent surgical treatment.

DR JEFFES: The ultimate goal is to reduce the number of SCCs over the patient's lifetime. By using therapies to eliminate AK, the risk of full-blown SCC is reduced. Without treatment, AK will progress to SCC for one in every 100 to 500 patients.⁴ What is more, photodamage-induced SCC metastasizes at the rate of 1% to 3%.⁵

DR KATZ: Younger and younger people visit dermatologists for treatment of sun-damaged skin. Although skin cancer is not the primary concern for these individuals, their concerns about skin aging are highly motivating. Although medical management begins with educating patients about sun avoidance and protective clothing and sunscreens, these patients will embrace photodamage therapies as long as inflammation is not unreasonable.

Topical Agents

DR JEFFES: The first topical therapy for AK, 5.0% 5-FU cream, has been available for almost 30 years. Other products, including 0.5% 5-FU cream in a microsphere, 1.0% and 2.0% 5-FU creams, 5.0% 5-FU solution, 3.0% diclofenac sodium gel, and imiquimod have been introduced. These drugs appear to have comparable efficacy when evaluated immediately posttherapy, but treatment durations differ. The 5.0% 5-FU products typically are applied for 2 to 4 weeks, whereas diclofenac is used for 2 to 3 months and imiquimod, 4 months. All of these topical agents induce skin irritation.

DR TANGHETTI: How do the 5-FU concentrations compare in efficacy and skin irritation?

DR JEFFES: Results from a recent study concluded that 0.5% 5-FU cream once daily was at least as effective as 5.0% 5-FU cream twice daily in terms of percent reduction and total clearance of AKs, and it was more

effective than the 5.0% cream in reducing absolute number of lesions from baseline.⁶ All patients experienced facial irritation, but fewer patients treated with the 0.5% cream reported symptoms.

DR TANGHETTI: How do the two 5-FU concentrations compare over the long run?

DR JEFFES: A more durable response results from 5.0% 5-FU applied aggressively. When it is applied twice daily for 4 weeks, the response lasts for 3 or 4 years; when applied for only 2 weeks, retreatment after a shorter posttherapy interval will be necessary. The duration of this posttherapy interval seems to depend on the magnitude and duration of inflammation as well as the degree of sun protection a patient practices, but AKs recur more rapidly following treatment with 0.5% 5-FU than with 5.0% 5-FU.

DR TORRES: Some patients do not remain clear of AK for more than 3 to 5 years after 5.0% 5-FU twice daily for 4 weeks. The lesions that develop in the treated area may be new or recurrent. If subclinical lesions are destroyed with field therapy, why would lesions recur? Big, thick lesions are more effectively treated by freezing or curetting them before treating with 5-FU. Any hypertrophic lesions persisting after 5-FU therapy are biopsied.

DR JEFFES: Persuasive data confirm that thicker AKs do not respond as well as thinner ones to any type of therapy.⁷ Also regardless of therapy type, including photodynamic therapy (PDT) and 5-FU, AKs on the head and neck seem to respond better than those at other sites, such as dorsal arms and hands.⁸

DR KATZ: Since field therapy aggressively prevents progression of AKs to

invasive SCC, it should be considered even in young patients. Moreover, many young patients exhibit much more subclinical damage than might be expected.



“The ultimate goal is to reduce the number of SCCs over the patient’s lifetime. By using therapies to eliminate AK, the risk of full-blown SCC is reduced.”
—Dr Jeffes

DR SKIDMORE: Some patients with multiple AKs clearly exhibit extensive photodamage. Their skin tells the dermatologist that their immune systems are losing the battle against skin lesions. When patients need a large field effect, 5-FU is the treatment of choice, especially on the arms.

DR TANGHETTI: What sorts of cutaneous effects can a patient expect with a typical 5-FU treatment course?

DR JEFFES: When patients apply 5.0% 5-FU cream twice daily for 4 weeks, lesions become erythematous, with erosions and scaling. Inflammation typically begins the second week of therapy and persists for 3 weeks. The severe inflammation resolves within 3 to 4 weeks after drug discontinuation. Thus, the duration of cosmetic problems is 6 to 7 weeks for a classic 4-week, twice-daily treatment routine. Although this regimen usually results in many years without any AK, patients will not tolerate looking less than optimal for more than 2 weeks.

DR WERSCHLER: When AK appears on cosmetically sensitive areas, such as the face, scalp, or neck, another noteworthy consequence of unsightly skin inflammation is absenteeism from the workplace due to simple embarrassment. Perhaps 5-FU should *not* be used twice daily for 4 weeks to treat AKs. Whatever AK is, precancerous lesions or carcinoma in situ, it is *not* invasive carcinoma.

DR SKIDMORE: Dermatologists should explain to patients that there

Figure:



Caption - Lawson

are two or three therapeutic options and be straightforward about which option is clinically preferable in each case. Based on the dermatologist's evaluation of the patient's skin and degree of photodamage, the physician can reasonably predict how the patient's skin will react to 5-FU, tailoring the intensity of treatment.

Mechanisms of Topical Action

DR JEFFES: There are no definitive, controlled studies concluding whether inflammation is required for effective eradication of AKs with topical therapy, but available studies suggest a correlation, albeit an imperfect one, between erythema and efficacy.^{6,9}

DR WERSCHLER: Inflammation may not be the primary mode of 5.0% 5-FU action. Perhaps 5-FU triggers inflammatory effects to which the immune system responds with secondary erythema. Or maybe 5-FU produces a true chemotherapeutic effect involving inflammation.

DR JEFFES: Both mechanisms might be working simultaneously. The chemotherapeutic effect would kill the hyperproliferative keratinocytes in AKs, as has long been suggested, but this may lead to an immune- or inflammation-mediated effect as well. Imiquimod and 5.0% 5-FU essentially have the same mechanisms of action but 5-FU starts out working as a chemotherapeutic antimetabolite and then mediates inflammation through cytokines at a secondary stage, whereas imiquimod binds directly to the tau-like protein, thereby inducing the inflammatory response directly.

DR WERSCHLER: A cytokine response clearly follows the metabolite response with 5-FU. If this cytokine



“Based on the dermatologist’s evaluation of the patient’s skin and degree of photodamage, the physician can reasonably predict how the patient’s skin will react to 5-FU, tailoring the intensity of treatment.”

—Dr Skidmore

response (secondary inflammatory response) is blocked, will AK destruction still result? When steroids are used to block the inflammation, AK destruction remains successful.

DR KATZ: A major inflammatory response is unnecessary for effective AK treatment according to studies reported years ago.¹⁰ When patients applied either 5-FU alone or in combination with steroids to inhibit inflammation, comparable reductions

in AKs resulted in the two treatment groups.

DR TANGHETTI: Why does an antimetabolite drug cause inflammation?

DR JEFFES: No one knows for sure. One can speculate that 5-FU is a false metabolite inducing apoptosis in hyperproliferative neoplastic keratinocytes in AKs, which, in turn, triggers a cytokine release followed by an inflammatory and/or immune response.

DR TORRES: If you use an antimetabolite effect with 5-FU while minimizing inflammation with concomitant steroids, how is efficacy affected?

DR TANGHETTI: It seems that we get the best clinical response in patients who develop the most significant inflammation. It is unclear if the use of topical steroids to lessen inflammation will compromise the benefits of topical therapy.

Managing Inflammation

DR KATZ: 5.0% 5-FU is considered the gold standard for field therapy of

Figure:



Caption - RAB

AK, and it produces significant inflammation. Dermatologists must find ways to manage the inflammatory response.

DR JEFFES: Duration and frequency of application determine degree of irritation as well as clearance rate. Reducing the application frequency is one reasonable approach to control the inflammatory response. For example, application of 5.0% 5-FU once daily for 2 to 4 weeks proves erythrogenic but effective in eliminating AKs.

DR TORRES: Dermatologists should not follow a cookbook approach with any topical agent; treatment must be titrated individually. People



“Patients tolerate inflammation of exposed body parts much less than on skin usually covered with clothes.”

—Dr Katz

with the fairest skin and most extensive photodamage are likely to experience more robust inflammatory reactions. In those cases, therefore, treatment may be initiated slowly with pulse therapy, treating twice weekly, to avoid irritation; alternatively, aggressive twice-daily treatment may be reduced to once daily or once every other day when inflammation develops. Furthermore, a major inflammatory response convinces some patients that the medicine is working.

DR JEFFES: Pulse therapy seems to stimulate less inflammation but may⁹ or may not¹¹ compromise efficacy. When treating AK on the face, most dermatologists titrate the dose to control the amount of erythema generated. Because of severe inflammation, patients with fair skin (Fitzpatrick type I) may be treated for only 1 or 2 weeks when a rest period is needed before therapy can continue. In contrast, patients with darker complexions may develop only mild, splotchy erythema with 4 to 6 weeks of treatment. Most patients, however, experience erythema for 2 weeks when 5.0% 5-FU cream is applied twice daily for 2 weeks; skin irritation becomes noticeable by the second week and continues for 1 week after drug dis-

continuation. For these patients, a rest period of 1 to 3 months precedes a second 2-week cycle of 5.0% 5-FU, resulting in substantial clinical improvement. Erythema during the second cycle is less than that during the first cycle.

DR SKIDMORE: Low-dose, long-pulse therapy with 5-FU is particularly useful in Florida, where patients with many AKs are common. In some cases, isotretinoin is used. Imiquimod is useful when cosmetic concerns are important or a patient develops allergic contact dermatitis to 5.0% 5-FU. For those needing extended therapy with 5-FU, follow-up with glycolic acid, topical retinoids, or a trichloroacetic acid peel can help cosmetically.

DR KATZ: Patients tolerate inflammation of exposed body parts much less than on skin usually covered with clothes. Although a fluor-hydroxy pulse peel can be applied to any area of skin, weekly application of glycolic acid and 5-FU for 8 weeks cleared facial AKs as effectively as nonpulsed 5-FU without the usual morbidity.¹² Not only does this combination clear AKs, but also the alpha-hydroxy acid peel improves the overall skin appearance.

DR TORRES: Topical antibiotics should be avoided during 5-FU therapy because they increase the likelihood of developing a sensitizing reaction. Wounds heal faster when they are covered with a moisturizing occlusive dressing, and plain petroleum jelly is ideal. If any extreme inflammatory reaction develops, a topical steroid may help calm the irritation.

DR SKIDMORE: Ointments are crucial to healing after 5.0% 5-FU therapy and petroleum jelly works as well as topical antibiotics without sensiti-

**Table 1:
Treatment Options
for Actinic Keratosis**

DESTRUCTIVE

- Cryotherapy with liquid nitrogen
- Photodynamic therapy with blue fluorescent light, pulsed-dye laser, or intense pulse light
- Curettage/excision
- Dermabrasion
- Chemical peel
- Laser

TOPICAL

- 0.5% 5-fluorouracil in microsphere vehicle
- 1.0% 5-fluorouracil cream or solution
- 2.0% 5-fluorouracil cream or solution
- 5.0% 5-fluorouracil cream or solution
- 3.0% diclofenac sodium gel
- Imiquimod
- Retinoids*

*Off-label investigational use.

zation risks. Acetic acid (0.25%) compresses are soothing and also promote healing after 5-FU treatment.

DR WERSCHLER: Acetic acid compresses are particularly useful when patients experience crusting, ulceration, or erosions. In addition, bland cleansers and moisturizers are helpful during and after 5-FU therapy.

DR JEFFES: Given that not all patients can tolerate 5-FU, second-line therapies are indicated occasionally. A 60- to 90-day course of 3.0% diclofenac gel may be useful for patients allergic to 5.0% 5-FU or who do not want the 5-FU-induced erythema. Although diclofenac is an effective treatment that produces less erythema than does 5-FU, the vast majority of patients just do not complete the long treatment course, so, from a practical standpoint, it becomes a less effective option.

DR TORRES: Diclofenac is most useful in patients who underwent a complete course of 5.0% 5-FU therapy 10 to 20 years earlier and now are reluctant to undergo a second course because of the skin irritation. Other diclofenac candidates include individuals whose occupations preclude considerable erythema, crusting, or scaling, such as models or cosmetics salespersons. However, care must be taken to avoid diclofenac in patients allergic to aspirin or any other nonsteroidal antiinflammatory drug.

Cheilitis

DR TANGHETTI: 5-FU, even in the lower concentrations, effectively destroys actinic cheilitis. However, because the affected lips are very sensitive to 5-FU, most patients stop applying even the 0.5% formulation after a single week because of the inflammation.



“It makes little sense to subject a patient with only a few lesions to a prolonged period of skin irritation caused by topical therapy. In this situation, therefore, cryotherapy is a more practical treatment option.”

—Dr Torres

DR TORRES: The lips are very sensitive. It is important for patients to apply an ointment to the lips to minimize dryness and fissures, which can be very uncomfortable.

DR JEFFES: Metastatic risk for general AK is about 1%. In stark contrast, however, metastatic risk is 10% when AKs are located on the mucous membranes of the lip. [please provide refs for 1% and 10%] Because of this high metastatic potential, aggressive therapy is warranted in actinic cheilitis. My patients are treated with 5-FU until full erosions on the lower lips develop (1 to 2 weeks), and, thereafter, vinegar soaks are recommended. Lips usually re-epithelialize within 1 week after the end of 5-FU therapy.

DR KATZ: Because of the high risk for metastasis, actinic cheilitis in my practice is treated with laser so that the epithelial layer can be completely destroyed, thus considerably reducing the metastatic risk.

Cryotherapy

DR TORRES: It makes little sense to subject a patient with only a few lesions to a prolonged period of skin irritation caused by topical therapy. In this situation, therefore, cryotherapy is a more practical treatment option. Following application of liquid nitrogen, lesions become irritated, ulcerate, and slough off as the cryotherapy wound heals.

DR SKIDMORE: When a patient presents with no more than 10 AKs, cryotherapy is a sound treatment choice although hypopigmentation remains an issue for patients with darker skin (ie, Fitzpatrick type IV or V). More than 10 AKs warrant field therapy with topical agents, especially since a big concern is the presence of subclinical lesions; field therapy manages both clinical and subclinical AK.

DR JEFFES: Patients with paler skin (ie, Fitzpatrick type I or II) are at highest risk for AK. However, because of their light complexions, cryotherapy-induced postinflammatory hyperpigmentation or hypopigmentation is not a major concern. Cryotherapy is effective for most AKs, but periodic monitoring for new or recurring lesions is recommended.

DR TANGHETTI: In summary, then, cryotherapy with liquid nitrogen is the most practical approach for managing a patient with only a limited number of AKs.

Photodynamic Therapy

DR JEFFES: A technique approved for treatment of hyperkeratotic AK of the face or scalp is PDT. Each AK is painted with 5-aminolevulinic acid (ALA), which converts to porphyrin that, in turn, destroys AKs when exposed to blue fluorescent light. As many as 15 AKs per patient were

treated in phase III trials where 84% of AKs completely cleared 8 weeks after a single cycle.¹³

DR KATZ: In my practice, ALA-PDT has been used as a field therapy for about a year. AKs are destroyed without substantial inflammation; patients develop erythema but no crusting. Rather than requiring the usual two office visits, short-contact ALA-PDT takes only 25 minutes altogether. ALA is applied with ultrasound for 15 minutes followed by 10 minutes of pulsed-dye laser. Although results are cosmetically satisfactory with minimal side effects, the treatment may be too expensive for some patients.

DR JEFFES: One advantage of ALA-PDT is that the maximum therapeutic effect is self-limiting because the porphyrin is destroyed during treatment. One disadvantage, which Dr Katz has overcome, is that two office visits are usually necessary, the first for ALA application and the second, 14 hours later, for porphyrin photoactivation. Burning and stinging may occur during photoactivation, but the discomfort is less than that with cryotherapy. Nevertheless, topical or local anesthesia may be desirable for treatment of many AKs or for field therapy of photodamage.

DR WERSCHLER: Although ALA-PDT works for AK, its real future probably lies in cosmetic dermatology for skin rejuvenation. It is unlikely to become the standard of care for AKs in a suburban dermatology office. Blue light, pulsed-dye laser, or intense pulsed-light equipment are not standard equipment for many practicing dermatologists.

DR SKIDMORE: Yes, several factors contribute to the expense of ALA-PDT. It requires added equipment, extra staff and time, and a dedicated treatment room. In addition, given

that patients generally must make two office visits, other therapies may be more economical.

DR TORRES: At our institution, ALA-PDT for AK destruction was not well received among patients. They did not like having to come back for a second office visit, and they often became concerned at the subsequent skin irritation.

DR TANGHETTI: In summary, ALA-PDT probably will not be used frequently although it does offer an advantage to patients who want effective treatment without cosmetic downtime.

Immunocompromised Patients

DR TANGHETTI: Topical 5.0% 5-FU and imiquimod are not effective for patients who are immunocompromised, usually by azathioprine or cyclosporine therapy. What can be done to enhance therapeutic response in those patients?

DR TORRES: Anecdotal reports suggest that combination therapy with 5.0% 5-FU and an immunomodulator, such as imiquimod, may be helpful.

DR JEFFES: Curettage and electrodesiccation are my first-line therapy for immunocompromised patients. Initially, shaved biopsies of the lesions, many of which are early SCC, are completed.

DR WERSCHLER: Transplant recipients develop many AKs and SCCs but immunocompromised patients do not mount as vigorous a response to 5.0% 5-FU as do individuals with competent immune systems. In my practice, lesions are treated first with cryotherapy and then with 5-FU. Once 5-FU has cleared the lesions, cryotherapy is repeated. Unfortunately, the lesions do not stay cleared for long, but transplant surgeons are nervous about imiquimod on large areas of skin.

DR SKIDMORE: Likewise, at the University of Florida, we have found that renal transplant recipients are not very responsive to 5.0% 5-FU treatment. However, transplant teams do not want imiquimod used on large skin areas.

DR TANGHETTI: So one prudent strategy might be to treat the AKs of immunocompromised individuals with a combination of cryotherapy

Figure:



Caption – Raffet

and 5.0% 5-FU and watch them frequently and closely.

Bowen's Disease

DR JEFFES: 5.0% 5-FU has proved more effective than curettage and electrodesiccation in the treatment of Bowen's disease, but lesions are very large, multifocal, and poorly demarcated, so dermatologists using curettage and electrodesiccation probably undertreat them. Patients should apply 5.0% 5-FU twice daily for 4 to 6 weeks, which is longer than 5-FU therapy for AKs. Because Bowen's disease arises from hair follicles located more deeply than topical therapies ordinarily reach, their depth of penetration is increased by occlusion with a band-aid. Instead of occlusion, the topical medication may be applied twice daily for 6 to 12 weeks.

DR TANGHETTI: Occlusion of Bowen's lesions may work like duct tape over a wart. Both duct tape and bandages trap bacteria, creating an inflammatory milieu. My patients with Bowen's disease apply 5.0% 5-FU twice daily for 8 to 10 weeks.

DR TORRES: For Bowen's disease, my patients apply 5.0% 5-FU for about 2 to 4 weeks to delineate margins. After 2 weeks of healing, any residual lesions are removed by curettage and electrodesiccation or excision.

DR SKIDMORE: Rather than topical therapies, cryosurgery generally is used for Bowen's disease in my practice. Imiquimod, however, works well for patients who want minimal scarring.

Superficial Multifocal Basal Cell Carcinoma

DR TANGHETTI: Superficial multifocal basal cell carcinomas (BCCs) are



“Superficial multifocal basal cell carcinomas (BCCs) are a challenge because they often occur on the back and chest, which are difficult surgical sites.”

—Dr Tanghetti

a challenge because they often occur on the back and chest, which are difficult surgical sites.

DR TORRES: These lesions can be surgically removed after they are shrunk by imiquimod pretreatment. Because results may be striking after the imiquimod therapy, some patients want to forego surgery, but cancer may remain without surgical excision. Even though 5.0% 5-FU is approved for the treatment of superficial BCCs, few dermatologists have been trained to use it for this indication.

DR TANGHETTI: I have found that 5.0% 5-FU for 10 to 12 weeks is an excellent therapeutic and cosmetic treatment for superficial multifocal BCCs.

DR SKIDMORE: Topical therapy is the best choice for BCCs on the central chest in women or the lower extremities in more mature adults because these sites do not heal well after surgery. When hypopigmentation is no concern, cryosurgery is another treatment option; it is rapid, the wounds heal reasonably quickly, and it is cost-effective.

DR JEFFES: I have been using 5.0% 5-FU for years to treat BCCs and have trained my residents to do the same. However, recurrence rates seem a bit higher following topical therapy than following surgery. My patients apply 5.0% 5-FU for up to 12 weeks.

Cost Considerations

DR TANGHETTI: Cost of therapy for AK varies and may be a consideration for some patients. Dermatologists offer patients treatment alternatives based on a number of factors already discussed by this expert

Figure:



Caption – Russel

panel—cost may be a criterion. For example, of the treatments discussed, I have found 5-FU to be the most economical one for patients.

DR TORRES: Imiquimod is a welcome alternative for patients who respond inadequately to 5-FU, but its cost is higher. One approach might be sequential therapy with 5-FU and imiquimod, which would eliminate lesions unresponsive to either therapy alone.

DR KATZ: As previously discussed, ALA is more expensive than the topical therapies. However, it is part of our treatment armamentarium for AK and may be appropriate for some patients.

DR SKIDMORE: Cost is one more reason to use destructive therapies when possible. Cryotherapy is less expensive than topical therapy when a limited number of AKs are present. Other less costly destructive therapies include curettage and electrodesiccation for hypertrophic AKs.

Conclusions

DR WERSCHLER: Field therapy is an essential part of the management of AKs, and, in my opinion, 5-FU is the cornerstone of AK management. It clears AK as well as photodamage, its side effects are manageable, its safety is well established, and its use is cost-effective.

DR TORRES: I agree that 5-FU is the gold standard for field therapy for AKs. However, now dermatologists have different treatments available, giving us more options for the management of patients.

DR JEFFES: Imiquimod, for example, offers an alternative to 5-FU, and both therapies are comparable in efficacy and side effects.



“...5-FU is the cornerstone of AK management. It clears AK as well as photodamage, its side effects are manageable, its safety is well established, and its use is cost-effective.”

—Dr Werscher

DR KATZ: Dermatologists will continue to find creative ways to use 5-FU in order to reduce its side effects. One approach is combination therapy. 5-FU should also be recommended to patients younger in age, both to prevent further AK development and to reduce existing photodamage.

DR TANGHETTI: In conclusion, we have reviewed many therapeutic options, both topical and surgical, for AK treatment. This expert panel has agreed that inflammation and wound healing remain challenges with the use of any topical therapy. Alternative topical therapies such as 3.0% diclofenac gel, imiquimod, and lower concentrations of 5-FU may be used. Dermatologists should consider use of cryotherapy or PDT when only a few AKs are present, but even in these cases 5.0% 5-FU plays a role as field therapy. The treatment of AK needs to be individualized. Dermatologists should review treatment options, their associated side effects, and comparable costs in devising a treatment plan for their patients.

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Advances in the Treatment of Verruca Vulgaris

Pediatric dermatologist Bari B. Cunningham, MD, has provided this roundtable discussion with important insights into the issues of treating warts in children. Because destructive therapy may not be appropriate for use in children, topical therapy with some of the same agents used to treat actinic keratoses (AKs) in adults are used on warts in younger patients.

—Emil A. Tanghetti, MD

Bari B. Cunningham, MD

Indications for Treatment

Warts are among the top-five most common skin conditions seen by dermatologists, and an estimated 10% of pediatric patients have warts. [Dr. Cunningham: Please provide reference if possible] The American Academy of Dermatology's treatment guidelines suggest several indications for wart removal, including patient wishes; symptoms such as pain, bleeding, itching, or burning; disfiguring or disabling lesions; immunocompromised patients; or patient desire not to spread the warts further on their own body or to others (see **Table 2**).¹ Some of the same modalities used on AK are used to treat warts in both children and adults (see **Table 3** on Page 13), and, as in treatment of AK in adults, problems arise.

Treatment Options

Although uncomfortable, the treatment of AK with cryosurgery is usually a tolerable and minor procedure. But for children, the experience of having liquid nitrogen applied to even a few warts can leave lifelong psychologic scars. In addition, destructive modalities have the potential to cause

scarring. Moreover, the location of the warts on a child's body influences our choice of treatment. One of the overarching concerns is to cause children no pain, if possible.

5-FU Treatment

The mechanism of action of 5-fluorouracil (5-FU) appears to be related to interference of viral replication and epidermal cell turnover. For the past 2 years in my dermatologic practice, I have been using 5.0% 5-FU to treat warts in children. Findings from a study soon to be published show that 88% of warts in our group of 39 children 4 to 18 years of age showed substantial reduction in wart size and thickness

at the end of 6 weeks of treatment with 5.0% 5-FU cream.

Study Design

We treated the warts with 5.0% 5-FU cream once or twice daily for 6 weeks. The cream was applied to the warts after they had been filed or pared, and then duct tape was applied as occlusion. There are data showing that duct tape alone applied to warts after filing may reduce their thickness and size.² The combined use of 5.0% 5-FU and duct tape seems to enhance the beneficial effects of each individual treatment.

Assessment of Side Effects

Because we applied a chemotherapeutic agent to vascular warts, we were

Table 2: Guidelines for Wart Treatment

- Patient desire for treatment
- Symptoms: pain, bleeding, itching, burning
- Disabling or disfiguring lesions
- Immunocompromised patients
- Prevention of spread on selves or others

Source: Drake LA et al. Guidelines for care of warts: Human papillomavirus. Committee on Guidelines of Care. *J Am Acad Dermatol.* 1995;32:98-103.

concerned that there was the potential for adverse side effects, particularly systemic absorption of the 5-FU. However, at the end of therapy, 38 of 39 children had nondetectable levels of 5-FU in blood, and one child had trace levels. Moreover, there were no changes in the complete blood count in any of the 39 children. Treatment with 5.0% 5-FU was well tolerated and considered painless by the vast majority of patients. We are now following these children for 6 months to document whether their warts recur and, if they do, at what rate.

Risk of Scarring

There are certain caveats about the use of 5.0% 5-FU in children. For one thing, it should not be used on the face. Although 5.0% 5-FU does not cause scarring when used to treat facial AK in adults, there is a risk of scarring when it is used on the face in children. We use 5.0% 5-FU only on the hands and feet.

There are other restrictions on the use of 5.0% 5-FU. I would not use it in the periungual location because it can penetrate the nail matrix, causing a temporary chemical onycholysis that parents find distressing. Nor should 5.0% 5-FU be used in thumb suckers because these children are at risk for ulcers and irritation of the mucosa of the lips as well as systemic absorption. Because 5.0% 5-FU is a category X drug, it should not be used in pregnancy.

Other Destructive Therapies

Pulsed-dye lasers, once popular for destruction of warts, are used less frequently these days. The treatment is painful both during therapy and post-



“Those who have numerous warts have a genetic variability in how their immune systems respond to the virus. Topical therapy is appropriate for these children.”

—Dr Cunningham

treatment. The efficacy of laser removal does not appear to be greater than that of standard therapy, and there have been reports of scarring. Some of the earliest destructive therapies for warts, aside from liquid nitrogen, were salicylic acid and filing or paring the warts. One newer treatment is imiquimod, which does not seem to

Table 3: Treatment Options for Warts

- Cimetidine
- Levamisole
- Cimetidine plus levamisole
- Duct tape
- Immunotherapy with imiquimod, squaric acid dibutylester, diphencycloproprone, or intralesional Candida antigen
- 5.0% 5-fluorouracil cream

Source: Bari B. Cunningham, MD

pose a risk of scarring on the face in children, and thus may be useful as an adjuvant therapy for facial warts.

Children can present with 50 to 60 warts in a field distribution. At least 99% of these children have competent immune systems. Those who have numerous warts have a genetic variability in how their immune systems respond to the virus. Topical therapy is appropriate for these children.

Conclusions

Some aspects of wart treatment in children differ from their management in adults. Children are less tolerant of painful procedures, which makes it impractical and ill advised to use cryotherapy, lasers, and other painful procedures as first-line therapy. Painless, effective therapies for the treatment of warts in children are desperately needed.

Topical therapy with 5.0% 5-FU has been shown to be effective in the management of warts in children. The drug, which is used as a chemotherapeutic agent in adults, is well tolerated and does not seem to have toxic effects when applied topically to children, even when used under occlusion. It can be used to safely and effectively treat warts on the hands and feet with no risk of scarring.

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The SKIN & ALLERGY NEWS supplement “Clinical Dialogues: Actinic Keratosis and Other Nonmelanoma Skin Cancers” is recognized by the American Academy of Dermatology for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology’s Continuing Medical Education Award. There is no fee for this activity. If you wish to receive CME credit, please mail or fax a photocopy of this completed form to SKIN & ALLERGY NEWS before May 31, 2005.

Course No. xxx-xxx, SKIN & ALLERGY NEWS, 60 Columbia Road, Bldg. B, Morristown, N.J. 07960-4526 (973) 290-8200 (973) 290-8250 Fax

Instructions: For each question or incomplete statement, one answer or completion is correct. Seven of 10 correct responses are required for credit. Circle the most appropriate response.

- Which skin type is most susceptible to AK but least susceptible to hypopigmentation from cryotherapy with liquid nitrogen?
 - Fitzpatrick type I
 - Fitzpatrick type II
 - Fitzpatrick type III
 - Fitzpatrick type IV
 - Fitzpatrick type V
- Which patients may be candidates for AK therapy with diclofenac?
 - Patients who are allergic to aspirin.
 - Patients taking oral nonsteroidal antiinflammatory drugs.
 - Patients who are unlikely to comply with a long course of therapy.
 - Patients whose occupation makes them unwilling to undergo significant inflammation during treatment for AKs.
- Which of the following statements about inflammation and AK clearing is not true?
 - The dose and length of treatment determine the amount of inflammation experienced by a patient.
 - The inflammation that occurs with 5-FU is probably both a primary and a secondary reaction to the treatment.
 - Decreasing inflammation with topical steroids totally negates the effectiveness of topical therapies.
 - Patients with the fairest skin are going to develop the most significant inflammation from topical therapy.
- Metastasis risk for general AK is about 1%; however, for AKs located on the mucous membranes of the lip, this percentage rises to:
 - 5%
 - 7%
 - 10%
 - 12%
- The finding strengthening the likelihood that AK is an early noninvasive form of SCC is that:
 - The two lesions manifest the same mutations of the p53 gene.
 - The two lesions manifest the same mutations of the p16 gene.
 - The two lesions share a common T_H1 response.
 - The two lesions share a common T_H2 response.
- Which of the following is the overriding consideration in the choice of wart treatment in children?
 - The treatment should have a low risk for spreading the warts iatrogenically.
 - The treatment should not require repeat office visits.
 - The treatment should be as painless as possible.
 - The treatment should not involve elaborate wound care to be done at home.
- The risk that SCC arising from photodamaged skin will metastasize is in the range of:
 - 0% to 0.5%
 - 1% to 3%
 - 5% to 7%
 - 10% to 12%
- How does occlusion work to enhance efficacy of a topical medication, as in the treatment of Bowen’s disease?
 - It increases the inflammatory milieu by trapping bacteria.
 - It decreases the risk for a sensitizing reaction.
 - It decreases hydration of the stratum corneum.
 - Occlusion does not change drug absorption.

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We would appreciate your answering the following questions in order to help us plan for other activities of this type.

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	Excellent	Good	Fair	Poor
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