

# Immune Response Modification: A New Paradigm for the Management of Actinic Keratoses and Nonmelanoma Skin Cancers



## HIGHLIGHTS OF A CLINICAL ROUNDTABLE

### Introduction

### Mechanisms of Action of Field Therapies

### Exploring the Evidence for Immune Response Modification in the Immunocompromised Patient Population

### Efficacy of Field Therapy for Actinic Keratosis

### Basal Cell Carcinoma and Invasive Squamous Cell Carcinoma: Evaluating the Options

### Judging Efficacy of Treatments for Actinic Keratosis

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# Immune Response Modification: A New Paradigm for the Management of Actinic Keratoses and Nonmelanoma Skin Cancers

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## Target Audience

This activity has been developed for dermatologists and other health care professionals who are involved in the treatment of patients with actinic keratoses (AKs) and nonmelanoma skin cancers—invasive squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs).

## Educational Needs

The incidence of actinic keratosis (AK)—increasingly recognized as squamous cell carcinoma (SCC) in situ—as well as SCC and basal cell carcinoma continues to rise in the United States. This is largely the result of greater numbers of individuals living longer lives; most have a long history of cumulative skin damage from ultraviolet light.

For isolated, discrete lesions that occur on areas of the skin other than the head and neck (typically areas of cosmetic concern to patients and physicians alike), cryosurgery or other destructive modalities may be considered as effective, relatively low-cost options for eliminating lesions. However, destructive modalities are not preferred when a lesion is present on the head or neck (because of the risk for hypopigmentation and/or scarring) or when a patient has multiple lesions on any given area of the skin (both for cosmetic reasons and for patient comfort). Moreover, it is now known that the occurrence of one or more AKs in a given area is a likely indicator of cumulative sun damage in that region of the skin, and that subclinical lesions are probably present. For these reasons, interest in so-called field therapy is increasing. Clinicians must remain up-to-date on the

results of laboratory and clinical investigations regarding field treatments, including 5-fluorouracil, photodynamic therapy, diclofenac, and imiquimod.

## Learning Objectives

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

- Describe the concept of “field cancerization” and field therapy.
- List and describe the methods of field therapy for AKs and nonmelanoma skin cancers, including 5-fluorouracil, photodynamic therapy, diclofenac, and imiquimod.
- Explain the mechanisms of action (where these are known) of the field therapies currently used or under investigation for AKs and nonmelanoma skin cancers.
- Discuss the results from well-controlled clinical trials concerning the efficacy, safety, and dosages of topical field therapies for AKs and nonmelanoma skin cancers.
- Explain the role of prophylactic therapy in managing patients with cumulative photodamage.

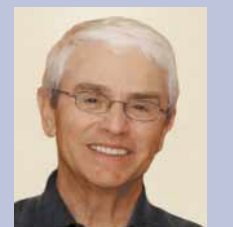
## Faculty Disclosures

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 Gaspari** is a consultant to 3M Pharmaceuticals. **Dr Jorizzo** is on the Speaker's Bureau at 3M and Dermik Laboratories, Inc. He discusses the unapproved use of combination therapy including fluorouracil cream, 0.5%, and imiquimod. **Dr Lebwahl** has received funding for clinical trials and grants for speaking from 3M. **Dr Salasche** is a consultant to 3M. **Dr Shumack** has received funding for clinical research from 3M and Bioglan Pharmaceuticals. He discusses the unlabeled use of the investigational product imiquimod for the treatment of basal cell carcinoma. **Dr Stockfleth** is a consultant to 3M.

# Introduction

Stuart J. Salasche, MD, Chair



In this discussion, the faculty focuses on four main areas in the treatment of nonmelanoma skin cancers (NMSCs), particularly actinic keratoses (AKs), squamous cell carcinomas (SCCs), and superficial basal cell carcinomas (BCCs):

- The concept of skin “field cancerization,” which is the rationale for the use of topical medications to treat AKs (Figure 1)
- Differentiation among the currently available topical medications, specifically emphasizing the unique nature of immune response modifiers (IRMs)
- The compatibility of topical therapy with the most commonly used clinical approach, destruction of lesions with liquid nitrogen (cryotherapy)
- The specific relevance of the IRM imiquimod to clinical practice, given the results of clinical trials, including recently completed phase III studies.

## Clinical Significance of AKs

We currently face an epidemic of NMSC in the United States, with more than 1 million new NMSCs occurring each year.<sup>1</sup> The majority of these—about 80%—are BCCs and the remaining 20% are SCCs.<sup>1</sup> Approximately 2,000 deaths each year are caused by SCCs,<sup>1</sup> and this number will probably increase as the number of organ transplantations rise, and, therefore, the number of immunosuppressed individuals increases.<sup>2</sup> Although BCC does not represent a high risk for metastasis, BCC lesions are locally invasive and destructive, and the treatment of these lesions is associated with scarring and sometimes significant disfigurement.

The incidence of AKs in the Caucasian population is exceedingly high in areas that have high numbers of lighter-skinned individuals. In Australia, for example, some estimates are that 40% to 50% of people more than 40 years of age have had at least one AK.<sup>3</sup> Multiple studies from Canada, the United States, and Australia have indicated that the incidence of AK in the Caucasian populations ranges from approximately 11% to 26%.<sup>4</sup> It appears that AK results from a cumulative type of ultraviolet (UV) radiation exposure;

not surprisingly, therefore, the number of AKs (and the number of SCCs) tends to increase with increasing age.<sup>4</sup>

The development of an AK should be considered to be a relatively late event in the carcinogenesis pathway leading to obvious skin cancer. Data from epidemi-

**The development of an AK should be considered to be a relatively late event in the carcinogenesis pathway leading to obvious skin cancer.**

ologic studies suggest that SCCs can develop from preexisting AKs, but also that there is a strong possibility that SCCs develop de novo in the photodamaged skin surrounding clinically apparent AKs. This means that the AK is one of the strongest markers we have to identify individuals who are prone to develop skin cancer, both by virtue of their previous cumulative exposure to UV radiation and their genetic predisposition to malignant changes in skin cells in response to this exposure.

## The Relationship Between AKs and SCCs

Multiple studies have demonstrated the strong relationship between AKs and SCCs. From this research, the conclusion can be drawn that there is very likely a spectrum of events that occurs when UV light hits the skin and causes damage to the DNA in cells that reside in the epidermis—specifically, in the case of AKs and SCCs, the keratinocytes. It has been shown that, with repeated episodes of UV exposure, the DNA is damaged in the form of thymine dimers; over time, these cannot be repaired by the immune system. The same dimers occur in the p53 oncogene, leading to mutations that may affect cell replication and regulation, ultimately leading to expanded clones of mutated cells. As the local immune response of the skin becomes progres-

sively more damaged by additional sun exposure (commonly called “UV hits”), the body is not able to rid itself of these transformed cells, and clones of these cells begin to grow. Over time, clinical lesions appear in the form of AKs and invasive SCC. The process seems to be particularly accelerated in individuals who are immunosuppressed.

AKs and invasive SCC share some common features. The risk factors are the same: patients are generally Caucasian with a history of excessive sun exposure. In terms of cellular biology, the DNA markers are often the same. Histologically, the same changes are seen. Starting at the dermal-epidermal junction, the keratinocytes begin to lose their polarity, resulting in larger cells that develop atypical nuclei. Over time, these changes are seen through the full thickness of the epidermis. Eventually, these same anaplastic cells break through the basement membrane into the dermis, resulting in invasive SCC with the potential for metastasis.

In patients with a significant amount of photodamage and clinically evident AKs, it has become evident that the surrounding skin shares the characteristics just described because of the presence of expanded clones of transformed dysplastic cells and subclinical AKs. These nascent lesions may regress spontaneously, may remain stable (in a state referred to as an intermediate end point), or may progress to AKs. The natural his-

**Figure 1. Multiple AKs of the Scalp**



Field therapy—alone or combined with lesion-targeted treatment—should be considered, particularly when multiple lesions are present (“field cancerization”), as on this patient’s scalp.

tory of subclinical lesions is unpredictable; however, the value of treating these areas as part of topical field therapy is intuitive.

Studies with topical medications, particularly with imiquimod, have demonstrated support for this concept of field cancerization and for the wisdom of field treatment when lesions are identified. In these studies, applications of topical medications have resulted in subclinical lesions being exposed—as with the baseline AKs, they become inflamed (in common parlance, they “light up”), become clinically apparent, and respond to therapy.

### Opportunity for Intervention

In addition to the mere presence of AKs, the risk for SCC increases with how long AKs have been present and with increased sun exposure. In addition, the number of AKs a patient has affects the risk for SCC. As the **Table** shows, the relative risk increases dramatically with increasing numbers of AKs in a given anatomic area (**Figure 2**). A clinician who observes a photodamaged area of skin with clinically apparent AKs has an opportunity not only to treat one of the late events of photodamage—that is, the AK—but also to address the entire photodamaged area as being sun-diseased and one that needs to be treated therapeutically. Such treatment—field therapy—is possible with the advent of topical medications that are effective and safe. In time, the development of innovative dosing regimens will, hopefully, make it more user-friendly.

**Table. Skin Cancer Risk Stratified With Baseline Number of Actinic Keratoses (AKs)**

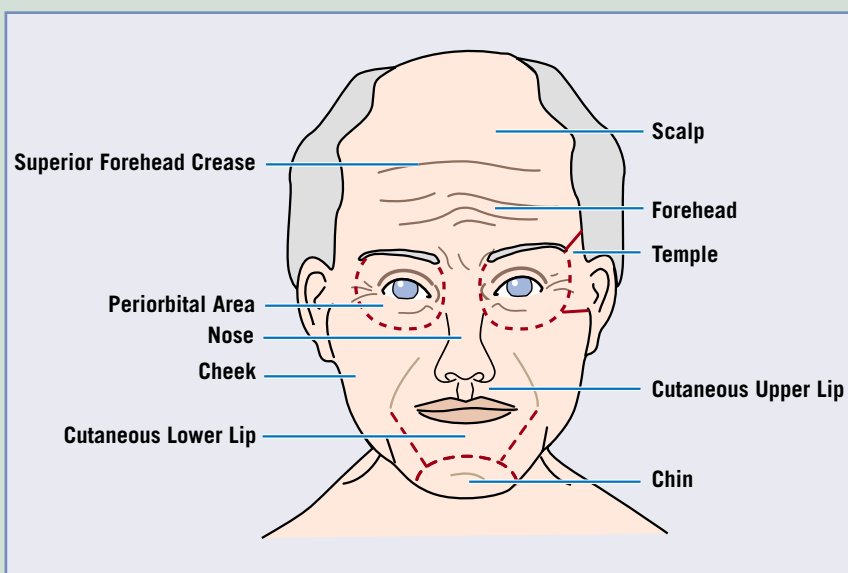
No. of AKs	Relative Risk
5 or fewer	1.0
6 to 20	4.0
More than 20	20.0

**Source:** Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer*. 1990;15:356-361.

**Figure 2. Cosmetic Units for Field Therapy**

The concept of dividing the face into anatomic areas, which have come to be known as cosmetic units, had its origins in reconstructive surgery. It was observed that areas separated by natural junction lines (such as the mentolabial crease, which divides the lower lip from the chin) frequently share common characteristics. These characteristics include pore size, elasticity, thickness, coloration, and number of hair follicles.

This concept is being adopted by those who study and use topical treatment (or field therapy) for actinic keratoses (AKs). Clinical investigators have found that it is easier to study the effect of a topical medication within a confined area, like the forehead or the cheeks, for two main reasons. First, the number of lesions before and after treatment is easier to determine in a well-defined region. Second, it has been observed that the skin in different regions reacts in a slightly different way to topical field treatments for AKs: differences have been noted between the forehead, scalp, cheek, neck, and the backs of the hands. As a result, recommendations for dosing regimens (frequency and duration) are likely to be developed based, in part, on the responses of each cosmetic unit.



### Summary

The continuum concept of AKs in relation to SCC is a relatively recent one, but increasing evidence supports the fact that AKs are a relatively late event in the photocarcinogenesis story. When AKs appear, it is a sign that damage already has been done in surrounding skin and that this skin contains many clones of transformed cells. Thus, although an AK lesion is not an obligate precursor to SCC (because it may also regress or may remain stable as an intermediate end point), all AKs should be treated in some manner.

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# Mechanisms of Action of Field Therapies

Anthony A. Gaspari, MD



The goal of lesion-targeted therapy for actinic keratoses (AKs) is to destroy visible, discrete lesions in a manner that is most effective, efficient, and comfortable for the patient. The goal of field therapy is to eliminate both visible AKs and those lesions that are subclinical and below the threshold of detection using conventional methods. The two types of treatments are compatible and, in fact, work synergistically on certain lesions. Some examples include elimination of hypertrophic AKs of the forehead, scalp, or dorsum of the hand using a destructive therapy such as cryosurgery, and a field therapy such as imiquimod to treat more diffuse, subtle lesions in the same field. This article reviews the mechanisms by which the currently available field therapies—imiquimod, 5-fluorouracil (5-FU), diclofenac, and others—are thought to work (Table).

## Immune System Damage in the Skin: A Brief Overview

The current theory explaining the progression of AKs to nonmelanoma skin cancer (NMSC) involves a combination of two major damaging events resulting from an accumulation of ultraviolet (UV) light exposure. One event is the accumulation of mutations in critical genes in epidermal keratinocytes. The second is both direct and indirect effects of UV light on the immune system in the skin that causes defects in normal immune surveillance.

It is now well recognized that a critical gene that is affected early in both AK and squamous cell carcinoma (SCC) lesions is the p53 gene, known as the “guardian of the genome.” Normally, when damage occurs to a cell’s DNA, this gene detects that damage and triggers apoptosis, or programmed cell death. Harris<sup>1</sup> demonstrated that UV light can damage the p53 gene, so that it fails to initiate apoptosis in cells with a damaged genome.

UV light exposure also can affect another critical set of genes, the ras oncogenes. UV-induced genetic changes in these genes can cause the development of pre-malignant clones with an enhanced survival advantage. These cells can undergo clonal expansion with further exposure to UV light, and AKs—either clinically apparent or subclinical—may result.<sup>2,3</sup>

With additional exposure to UV light, other genetic abnormalities can accumulate in the affected cells. These abnormalities are known to cause progression from sun damage to the development of AKs and, ultimately, to the manifestation of SCC.

The central immunocyte affected by UV light is the epidermal Langerhans’ cell. Normally, Langerhans’ cells can activate the subset of helper T cells known as T<sub>H</sub>1. After being activated by antigen-presenting cells such as Langerhans’ cells, T<sub>H</sub>1 cells produce interferon-gamma. However, when Langerhans’ cells are damaged by UV-light exposure, they become deficient in this host defense, antigen-presenting pathway<sup>4</sup> and instead tend to activate T<sub>H</sub>2 cells, the T-cell subset responsible for the production of interleukin (IL)-4, leading to excessive activation of suppressor T cells.<sup>5</sup>

## Imiquimod

Evidence to date has demonstrated that imiquimod triggers expression of a variety of cytokines that initiate innate immunity and have the ability to interface with adaptive immunity. As a result, these broad-spectrum cytokines can influence and shape immunity. Both preclinical studies, chiefly in the mouse model, and clinical studies have shown that imiquimod has antiviral activity and anti-tumor activity.

Imiquimod targets innate immunity—that is, monocytes, macrophages, and antigen-presenting cells via the nuclear

factor (NF) kappa B signaling pathway—resulting in the triggering of a wide array of cytokines. In addition, imiquimod has been shown to trigger maturation and cytokine production in epidermal Langerhans’ and other dendritic cells. The Langerhans’ cells are thus transformed from a resting state to a migratory state—that is, they leave the tissue and present to the local immune system, the regional lymph nodes. When these activated Langerhans’ cells interact with T cells, they are capable of activating the T<sub>H</sub>1 subset, not only because of the cytokines but also because of the new upregulation of molecules that are important for antigen presentation. These include the class I major histocompatibility complex (MHC), class II MHC, and the costimulatory molecules, all of which are important for cell-cell interactions that lead to effective antigen presentation to CD4+ and CD8+ T cells.

In addition, it has been demonstrated that imiquimod targets at least one of the Toll-like receptors (TLRs), TLR-7, in the innate immune system. The major role of TLRs is to recognize the presence of microbial molecules. The stimulation of TLR-7 by imiquimod “tricks” the immune system into recognizing and responding to what it perceives as a viral or bacterial infection.

## 5-Fluorouracil

Topical 5-FU is a pyrimidine analog that is incorporated into the cell’s DNA because of its structural similarity to

Table. Summary: Field Therapies for Actinic Keratoses

AGENT	MECHANISM OF ACTION
Chemical peels	Physical removal of photodamaged skin
Dermabrasion	Physical removal of photodamaged skin
Diclofenac sodium	Unknown, but theoretically, inhibition of cyclooxygenase-2
5-fluorouracil	Cytotoxicity
Imiquimod	Upregulation of cytokines important in innate immunity
Laser resurfacing	Physical removal of photodamaged skin
Photodynamic therapy	Preferential death of cells that convert aminolevulinic acid to protoporphyrin IX
T4 endonuclease*	Repair of damaged DNA

\* This agent is being used experimentally in the treatment of AKs.

uracil. The main mechanism of action of 5-FU is that it interferes with DNA synthesis by blocking conversion of deoxyuradilic acid to thymidylic acid.<sup>6,7</sup> Hence, cells that are rapidly proliferating—that is, cancer cells and initiated AK cells—will be targeted by its cytotoxicity. 5-FU causes the death of large numbers of proliferating, initiated premalignant cells, a process that is manifested clinically by inflammation. 5-FU has selective effects on damaged cells (the proliferating initiated cells). Because healthy, unaffected cells do not incorporate the 5-FU molecule, healthy tissue is more resistant to its inflammatory effects.

With 5-FU, the cure rate is highly dependent on the generation of inflammation, erosion, and ulceration, and some of these effects may be related to the concentration of the drug. In most patients, these effects resolve completely after causing only moderate discomfort, and the cosmetic outcome is good. About 3% of the general population has a deficiency of the enzyme dihydropyrimidine dehydrogenase, which can result in severe generalized cytotoxic reactions on systemic exposure to 5-FU.<sup>8,9</sup> However, topical 5-FU has rarely been associated with any local or systemic toxicity related to this enzyme deficiency.

Several different formulations now are available for 5-FU, and the formulation can affect the drug's ability to elicit inflammatory reactions in the skin as well as its efficacy.

## Diclofenac

Diclofenac sodium gel, 3%, is a topical nonsteroidal antiinflammatory drug (NSAID) that is applied to AK lesions twice daily for 2 to 3 months. The onset of action is somewhat delayed, but a significant number of patients—particularly those with lesions in the head and neck area—experience complete clearance of AKs within about 1 month after discontinuing treatment. The adverse effects associated with this therapy are local reactions that include contact dermatitis, rash, dryness, and exfoliation.

The mechanism of action of this drug is not known, but, based on what is currently known about other NSAIDs, it is possible to theorize that diclofenac's mechanism of action is related to the cyclooxygenase (COX) family of enzymes and their role in epidermal physiology and the pathophysiologic response of the skin to UV light exposure.<sup>10,11</sup>

COX-1, an enzyme that controls prostaglandin synthesis, is not modulated by UV light. COX-2 and cytosolic phospholipase A<sub>2</sub> are enzymes that are upreg-

ulated after UV-light exposure. COX-2 is responsible for increases in synthesis of prostaglandin E<sub>2</sub> and prostaglandin F<sub>2</sub>α. This is important for three reasons. First, these COX-2-mediated prostaglandins probably play an important role in UV-related erythema in the skin. Second, these prostaglandins play an important role in UV immunosuppression, in that prostaglandins adversely affect Langerhans' cell function. Third, they drive the proliferation of epidermal keratinocytes; initiated keratinocytes may be very responsive to clonal expansion as a result of chronic prostaglandin upregulation. Other experimental evidence shows that if COX-2 expression is inhibited using an antisense approach—that is, if COX-2 gene expression and upregulation are inhibited after UV exposure—then epidermal cell growth may be suppressed.<sup>12</sup> In sum, theoretically, by targeting COX-2, it may be possible to prevent some of the UV effects mediated by prostaglandins.

**...in a patient with AKs and NMSC, the risk for developing additional AKs or NMSC lesions and the potential for progression of AKs to SCC is ongoing.**

## Photodynamic Therapy

Photodynamic therapy (PDT), as approved for use in the United States, involves application of a 20% topical solution of aminolevulinic acid (ALA) to photodamaged and AK-bearing skin and, after 24 hours, exposing that area of the skin to a blue-light source. During this time, ALA is preferentially taken up by the initiated AK or SCC lesions and converted to protoporphyrin IX, a potent photosensitizer. Exposure to blue light results in the preferential death of cells that have converted ALA to protoporphyrin IX. Adverse reactions seen with PDT are related to severe phototoxic reactions, including stinging, burning, itching, erythema, edema, swelling, and exudation.<sup>13</sup>

## Other Field Therapies

Several other field therapies are of potential use in some patients with AKs. These include chemical peeling for the treatment of widespread actinic damage in the head and neck area. The depth

and degree of the inflammation related to the chemical peel is affected by the agent chosen, as well as the strength and duration of application and the clinician's experience. The chemical agents most commonly used include trichloroacetic acid, glycolic acid, resorcinol, Jessner's solution, and salicylic acid.

Dermabrasion is another approach, using a diamond fraise or a wire brush, to physically remove the outer layers of the epidermis. The depth of the dermabrasion is controlled by the clinician, so this is another field therapy that requires a great deal of expertise and experience to accomplish safely and to effect good results. Laser resurfacing is another technique that removes outer epidermal layers and, as with dermabrasion, requires a high level of skill to achieve the desired therapeutic goals.

Topical or systemic retinoids are agents that play a role in prophylaxis or may be used to enhance the benefits of other field treatments. These agents are not generally used as monotherapies because the topicals lack efficacy and the systemic drugs are associated with a risk for toxicity.

Finally, an evolving field therapy is the T4 endonuclease. This is a viral DNA repair enzyme that has been used to treat patients with xeroderma pigmentosum, who have marked photosensitivity and a high propensity for developing multiple skin cancers later in life. T4 endonuclease has been shown to have efficacy in these patients and is now being studied for the treatment of photodamage, including AKs.<sup>14</sup>

## Summary

Among the major field therapies currently available, imiquimod is unique in that it has cytotoxic effects but also locally recruits the immune system for the host defense against AKs and NMSC. 5-FU is a topical cytotoxic agent. The NSAID diclofenac probably inhibits UV-induced prostaglandin production. PDT relies on photosensitization and interacts with long-wave UV light to generate a phototoxic reaction.

Regardless of the methodology chosen to treat AKs, it is crucial for the clinician to develop and maintain a long-term relationship with patients and to ensure that follow-up is ongoing, because, in a patient with AKs and NMSC, the risk for developing additional AKs or NMSC lesions and the potential for progression of AKs to SCC is ongoing.

In addition, patients with AKs must be taught that photoprotection is fundamental to reducing those risks. Finally, these

*Continued on page 14*

# Exploring the Evidence for Immune Response Modification in the Immunocompromised Patient Population

Professor Dr med Eggert Stockfleth



The incidence of nonmelanoma skin cancer (NMSC)—namely, basal cell carcinoma, actinic keratosis (AK), and invasive squamous cell carcinoma (SCC)—continues to increase worldwide. At the Charité Hospital in Berlin, Germany, our group is focusing largely on both primary and secondary prevention of AK, which we consider to be carcinoma in situ and an early stage of SCC.

As discussed in other articles in this supplement, the appearance of an AK does not indicate the presence of a single tumor; rather, it is a manifestation of a change in the field in which it occurs. The term “field cancerization” is a good one to describe what has occurred in an area of skin by the time an AK is clinically visible. The entire area surrounding an AK has been destroyed by photodamage, and biopsies in the region will demonstrate atypical keratinocytes and mitoses. Clinically, as well, it is sometimes extremely difficult to distinguish between benign and malignant lesions. In our immunosuppressed organ transplant patient population, these are referred to as “wartlike lesions” until they can be definitively diagnosed.

Investigators throughout the world have, within the past decade, described various reasons for the development of AKs. Our group is focusing increasingly on gene mutations. In addition, we are exploring the meaning of human papillomavirus (HPV) in skin cancer.

The rationale for linking these two areas is the high incidence of HPV detected in AKs and invasive SCC: in the non-immunosuppressed population, HPV is found in 40% to 50% of AKs and in up to 70% of SCCs.<sup>1,2</sup> Those numbers are even higher in immunosuppressed patients, mainly patients who have undergone organ transplantation. In this latter group, HPV is found in about 80% of these lesions.<sup>1,2</sup> Because of their high risk for developing skin malignancies, we are studying patients with organ transplants as a “model” to try to establish heretofore unidentified pathways by which benign warts undergo anaplastic transformation. The establishment of such pathways also may help explain the possible role of HPV in increasing the risk for the development

of large numbers of AKs in immunosuppressed patients as well as the progression of AKs to invasive SCC in all patients.

## Role of Immune Response Modifiers in Skin Immunity

We propose three main risk factors for developing NMSC: exposure to ultraviolet light, and the presence of HPV and dysfunction of the local immune system as possible cofactors.

It is well known that human immunity consists of innate and acquired immunity. Acquired immunity is responsible for cellular and humoral immunity, but it is mainly cellular immunity that is responsible for detecting virus-infected keratinocytes or tumor cells. This relies mainly on the response of the subset of helper T cells called T<sub>H</sub>1 cells, and, consequently, expression of several types of cytokines, including interleukin (IL)-2 and interferon (IFN). In addition, Toll-like receptors (TLRs) have been identified and have been shown to play a critical role in innate immunity.

Research has demonstrated that the immune response modifier (IRM) imiquimod has no direct antiviral or antitumor effect but that it can cause the expression of cytokines such as IFN- $\alpha$ , IFN- $\beta$ , and IL-8. More recently, it has been shown that certain TLRs, mainly TLR-7 and TLR-8, bind to IRMs. The binding of imiquimod to TLR-7 has been shown to result in the secretion of cytokines that are important in antiviral and anticancer activity.

Recently, our group initiated a double-blind, vehicle-controlled study to assess the safety and efficacy of imiquimod for the treatment of AKs in organ transplant recipients. In addition to those from our center, investigators from centers in Oslo, Norway, and Rome, Italy, are participating. In this study, patients apply the active drug or vehicle once daily, three times a week. The clinical results of this study will be supported by histologic evidence—biopsies are being taken before and after treatment.

## Surveillance of Organ Transplant Recipients

To date, we have registered approximately 70,000 patients in Germany who

have received organ transplants (mostly renal, heart, and liver transplants). In 2002 alone, we logged 5,000 patient visits in our department. We are following these patients carefully, and including data we are collecting in a network system we started in Europe known as Skin Care in Organ Transplant Patients (SCOP). Dermatology centers in other European countries where large numbers of organ transplant recipients are seen participate in SCOP. More recently, a network also has been instituted that includes centers in the United States, Canada, and Australia—the International Skin Cancer in Organ Transplant Patients Collaborative Group (ITSCC). Further information about SCOP can be accessed via the Internet Web site, [www.SCOPnetwork.org](http://www.SCOPnetwork.org); the Web address for ITSCC is [www.ITSCC.org](http://www.ITSCC.org). Both of these sites include information for physicians and patients.

## Conclusion

Research at our center continues to focus on further elucidating the mode of action of IRM therapy in organ transplant recipients. In addition, we are investigating possible pathways of inducing apoptosis, or programmed cell death, and how imiquimod may induce apoptosis.

Meanwhile, perhaps the most important clinical application of the evidence to date concerning the pathophysiology of photodamage is the concept of field cancerization. It has become clear that an AK or an SCC is not an isolated tumor but exists within an area of sun-damaged tissue that may or may not express clinically visible lesions in the future. By extension, acceptance of the concept of field cancerization means acceptance of the notion of field therapy.

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# Efficacy of Field Therapy for Actinic Keratosis

Mark G. Lebwohl, MD



Destructive modalities remain the most commonly used methods to treat individual actinic keratoses (AKs), and it is unlikely that these traditional therapies—cryotherapy, trichloroacetic acid, and electrodesiccation and curettage—will be replaced by any other method. Another traditional modality, the topical chemotherapeutic agent 5% 5-fluorouracil (5-FU), is still a common treatment for multiple AKs, particularly those that occur in cosmetically sensitive areas such as the scalp and face. Topical 5-FU does ultimately yield a good cosmetic outcome, but patients experience weeks of severe erythema, oozing, vesiculation, and crusting. As a result, new field therapy options have been explored.

## New Topical Treatments Introduced for AKs

A 0.5% 5-FU cream now is available and was tested for 1, 2, and 4 weeks of treatment.<sup>1</sup> The investigators noted that patients who used the cream on the face for 1 week had significant improvement compared with vehicle. Efficacy improved when the cream was used for longer periods, but most of these patients experienced mild to moderate facial irritation.

Diclofenac 3% gel is another relatively recent addition to the clinician's roster of AK treatments. Typically, at 30 days after starting therapy, patients experience inflammation of both apparent and previously nonapparent AKs. Marked improvement is seen after 90 days, with disappearance of inflamed AKs and resolution of the inflammatory reaction.

A treatment that has not become widely accepted in this country is photodynamic therapy (PDT).<sup>2</sup> The reasons for PDT's limited acceptance include the pain associated with the procedure as well as reimbursement issues associated with this relatively costly method. PDT may become more accepted in the United States in the future if these problems can be resolved.

The disadvantages and limitations associated with these topical AK therapies underscored the need for more treatment options. Clinicians in the field of dermatology are accustomed to exploring new uses of available topical agents, and a recent National Ambulatory Care Survey from Sugarman and colleagues<sup>3</sup> shows that AKs are managed with off-label prescriptions 52% of the time, second

only to acne rosacea, which is treated off-label 73% of the time. The immune response modifier imiquimod, originally approved by the US Food and Drug Administration (FDA) for the treatment of genital warts, has been used by many dermatologists to treat AKs for several years. This off-label experience led to several clinical trials and the recent FDA approval of imiquimod for the treatment of AKs.

**Clinicians in the field of dermatology are accustomed to exploring new uses of available topical agents... AKs are managed with off-label prescriptions 52% of the time, second only to acne rosacea....**

## Clinical Studies of Imiquimod for AKs

Persaud and colleagues<sup>4</sup> at Mount Sinai School of Medicine in New York City conducted a bilateral comparison controlled trial in which imiquimod cream was applied three times a week to one side of

the body and vehicle only was applied to a matched symmetrical site (primarily the dorsal hands and face) on the other side of the body. Imiquimod and vehicle were applied according to this schedule for 8 weeks. Subjects were assessed at weeks 2, 4, 6, 8, 12, and 16. A significant reduction was seen in the number of AKs on the imiquimod-treated side.

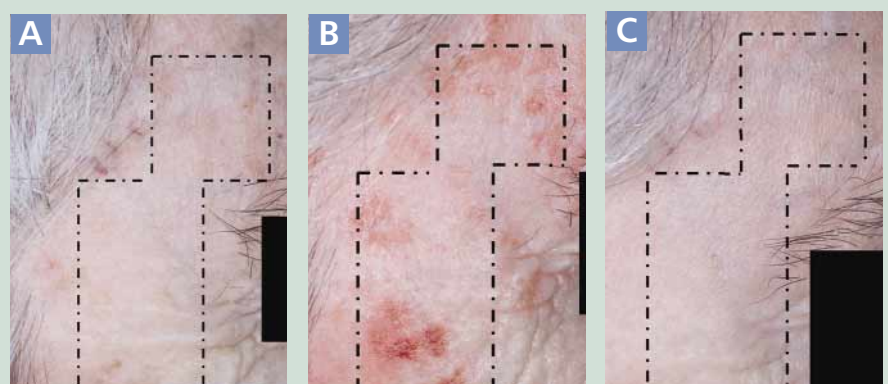
The results of this study prompted efforts to launch phase III studies of imiquimod in the treatment of AKs. The phase III studies were completed recently, and results are expected to be published in spring 2004. Meanwhile, it is possible here to provide a general discussion of those studies.

**Study Design Features.** The study design was randomized, double-blind, multicenter, vehicle controlled, and parallel group. The subjects were randomized to receive, in equal numbers, either imiquimod 5% cream or vehicle. The AKs were treated twice a week for 16 weeks.

**Achievement of Complete Clearance.** A significant number of subjects in the treatment group achieved complete clearance compared with the vehicle group. A subgroup analysis showed that more women than men achieved the primary end point, as did older patients. Sunscreen users did better than those who did not use sunscreens. Fitzpatrick skin type did not make a significant difference in response.

*Continued on page 15*

**Figure. Field Therapy Reveals Subclinical Lesions**



This patient was treated with imiquimod twice daily for 16 weeks. At baseline (A), the actinic keratosis (AK) lesion count in the treated area on the right temple was five; note the mild erythema, flaking, dryness, and scabbing in the area. By week 4 of therapy, the lesion count had increased to 10, which represents the "lighting up" of previously subclinical lesions (B). At 8 weeks posttreatment follow-up (C), the treatment area was completely clear of AKs and local skin reactions had completely resolved.

# Basal Cell Carcinoma and Invasive Squamous Cell Carcinoma: Evaluating the Options

Stephen P. Shumack, MD



Basal cell carcinoma (BCC) and invasive squamous cell carcinoma (SCC) are associated with significant morbidity and, in the case of SCC in particular, a risk for metastasis and death. These lesions also have the potential for causing permanent disfigurement and are an economic burden on the health care system. The main goal of treatment of these tumors is complete eradication with a minimum of risk for recurrence. Ideally, management options also should take into account the cosmetic outcome of therapy as well as patient preference. The currently available options are reviewed here, and summarized in the **Table** (on page 11).

## Cryotherapy

Cryotherapy is one of the ablative techniques that has been in common use for about the past 3 decades for superficial BCCs (it is not routinely recommended for SCCs). This usually involves a double freeze-thaw cycle of 30 seconds each, with a margin of about 5 mm around the tumor. The 5-year recurrence rate with this therapy is less than 9%.<sup>1,2</sup>

Among the main advantages of cryotherapy are that treatment is quick and convenient. In addition, cryotherapy is useful for the treatment of multiple BCCs, as in Gorlin's syndrome, because many lesions can be treated at the same time. Finally, this modality is beneficial for destroying BCCs that arise near the site of a nonmelanoma skin cancer (NMSC) previously treated with radiation.

Unless a pretreatment biopsy has been performed, there is no histologic evidence of the tumor, nor is there any histologic evidence of tumor-free margins. Another disadvantage is the significant inflammation, edema, and tissue damage associated with cryotherapy. This may lead to a long healing phase, which can persist for 1 to 2 months in some patients, depending on the size and the site of the treatment area.

Cryotherapy is less reliable—and, therefore, is not recommended—for the treatment of morpheic, infiltrative, or nodular BCC subtypes<sup>3,4</sup> or high-risk sites (lip, inner canthi, alar crease, or preauricular area).<sup>5,6</sup> The complications associated with cryotherapy include hemorrhage, sensory nerve damage (if it is performed over the track of a sensory nerve), and scarring. In addition, hypopigmentation,

which can be significant and permanent in some patients, usually occurs.

## Electrodesiccation and Curettage

Electrodesiccation and curettage (ED & C) for BCC and SCC, performed under local anesthesia, usually involves two to three passes with progressively smaller-sized curettes. These passes are interspersed with gentle electrodesiccation to manage hemostasis in the treated area and to eliminate some of the malignant cells that may extend beyond the curetted area.

The success of this technique is highly dependent on the skill of the operator; recurrence rates are typically much lower when ED & C is performed by clinicians who do the procedure on a regular basis. The reported overall 5-year recurrence rate for BCCs is about 6%,<sup>7,8</sup> and, for SCCs, it is about 5%.<sup>9</sup>

With BCCs, the main factors for selection of this modality are tumor site and size. ED & C is suitable for relatively small, primary (nonrecurrent) BCCs that are not morpheic in type. (Morpheic tumors are not easily curettable because of the lack of gelatinous stroma.) Opinion varies on the use of ED & C with SCCs, but it is being used more frequently in patients who develop many SCCs, such as transplant patients, in whom surgical excision is not practical. The technique is quite useful for well-differentiated and superficial SCCs as well as keratoacanthomas, particularly on areas where excision is difficult, such as the legs.

The advantages of ED & C include the availability of limited histology, and, like cryotherapy, ED & C is a relatively quick and convenient modality. On the down side, there is no specific margin control. Further, there is a risk of recurrence below scars. Therefore, a deep residual area of SCC can develop beneath a scarred area, and recognition of the recurrence can be delayed. Finally, the few patients with old pacemakers in place may experience interference of pacemaker activity from the ED & C equipment.

Scarring is a potential complication, with textural changes being more likely than with cryotherapy. Pigmentation changes may also result after ED & C, and leg ulcers may occur on the lower leg if circulation is impaired in that area. Tissue

contraction can lead to some deformity if this procedure is performed around certain cosmetically sensitive areas, such as the lip.

## Surgical Excision

Surgical excision with standard margins is the gold standard for both SCCs and BCCs. The cure rate for primary BCCs with a diameter of less than 1 cm and 4-mm margins is 98%,<sup>10</sup> and for tumors greater than 1.5 cm, the cure rate is 92%.<sup>11</sup> With SCCs, the overall cure rate is usually more than 90%,<sup>12</sup> although for well-differentiated tumors with a 4-mm margin, the cure rate is reported to be about 95%.<sup>13</sup> Similar cure rates for SCCs larger than 2 cm require 10-mm margins.<sup>14</sup>

Local recurrence is twice as likely for poorly differentiated SCCs,<sup>15</sup> and higher recurrence rates can be expected at certain sites such as the ear (19%) and lip (11%), which are also areas associated with a higher rate of metastasis.<sup>15</sup> Thus, these areas need to be treated more aggressively, with larger surgical margins and a more rigorous follow-up period. Patients who have undergone organ transplantation experience a marked increase—more than 100-fold compared with the general population—in the number of SCCs; the SCCs in these patients also are highly aggressive and more likely to metastasize.<sup>16</sup>

The main advantages of surgical excision with standard margins are superior cure rates and the availability of formal histology with margins to document tumor clearance. The surgical scar (sometimes hypertrophic or keloid-type scars) may be a disadvantage, and the complications associated with this modality are the same as for other surgical procedures: hematoma, bleeding, and infection.

## Mohs' Micrographic Surgery

Mohs' micrographic surgery is an extension of traditional surgical excision. It is primarily indicated for morpheic, infiltrative, and sclerosing BCCs; for recurrent BCCs and SCCs; for primary, nodular tumors > 2 cm; and for BCCs and SCCs in which perineural invasion is present. It also is employed in areas where maximum tissue conservation is required, such as around the eyes.

The 5-year recurrence rate for primary

BCCs treated with Mohs' micrographic surgery is about 1%<sup>1</sup> and, for recurrent BCCs, about 5%.<sup>17</sup> The use of this modality for SCC yields results consistently superior to those reported for standard excision.<sup>12</sup>

The main advantage of this technique is that it offers maximum tissue conservation with the lowest risk for recurrence. However, it does require special expertise and facilities, including specially trained support staff, and it is more time- and labor-intensive than standard surgery. The main complications are the same as those for standard surgery, as well as flap/graft failure.

### Laser Excision

Laser excision with cutting lasers is rarely utilized for the treatment of BCCs and SCCs. Ablative lasers—erbium and carbon dioxide lasers—are more commonly employed. The cure rates achieved are similar to those seen with ED & C.<sup>18</sup> The advantages of using a laser to elimi-

nate these tumors are more precise positioning and control of the tumor ablation, hemostasis (bleeding is minimal), and the ability to treat large numbers of lesions rapidly in a single session. In addition, laser excision is useful for difficult areas such as the vermilion of the lip and the digits. The cost of equipment and training and the dependence on operator skill are disadvantages that make laser excision impractical for widespread routine use for this indication.

### Phototherapy

Phototherapy is a modality that involves the selective uptake of a nontoxic photosensitizer by malignant tissue and subsequent light exposure—usually visible light. This results in a photochemical process that leads to preferential tumor destruction. Phototherapy is used topically with 20% aminolevulinic acid (ALA) under occlusion followed by exposure to a light source.

The success rate for superficial BCCs is about 85% to 90%,<sup>19</sup> and, for nodular BCCs, it ranges from 60% to 85%.<sup>20</sup> Some of these tumors require a repeat treatment about a month after the first for optimum results. The cure rate with SCCs is not as good, with success rates reported to be anywhere from 40% to 70%.<sup>21</sup>

Phototherapy has the advantage of providing a good cosmetic outcome. In addition, it can be a field treatment, so a number of lesions, including actinic keratoses (AKs), can be eliminated in a given treatment field. Phototherapy is also well suited for use in frail patients and in others in whom surgery would be contraindicated. Phototherapy is not effective for lesions that are markedly pigmented, such as pigmented BCCs.

Local anesthesia may be required because a patient may experience pain when the light is applied. Other disadvantages include a long preparation time for application of topical ALA and the incon-

**Table. Treatment Options for BCCs and Invasive SCCs**

METHOD/AGENT	INDICATIONS	COMMENTS
Cryotherapy	Superficial BCC	5-year recurrence rate, < 9%
ED & C	BCC and SCC	Overall 5-year recurrence rate is about 6% for BCC and 5% for SCC
Surgical excision with standard margins	BCC and SCC	<ul style="list-style-type: none"> <li>• Gold standard for both types of tumors</li> <li>• Cure rate for primary BCCs with a diameter &lt; 1 cm and 4-mm margins is 98%; for tumors with diameters &gt; 1.5 cm, the cure rate is 92%</li> <li>• For SCCs up to 2 cm in diameter the overall cure rate with 4-mm margins usually is &gt; 90%, but may be as high as 95% if tumors are well-differentiated; tumors larger than 2 cm require 10-mm margins for similar cure rates</li> </ul>
Mohs' micrographic surgery	<p>Morpheic, infiltrative, and sclerosing BCCs</p> <p>Recurrent BCCs and SCCs</p> <p>Primary, nodular tumors &gt; 2 cm</p> <p>BCCs and SCCs in which perineural invasion is present</p> <p>Tumors in areas where tissue conservation is important (eg, around the eyes)</p>	5-year recurrence rate for primary BCCs is about 1%, and about 5% for recurrent BCCs; results with SCC are consistently superior to those achieved with standard excision
Laser excision with ablative lasers (erbium and carbon dioxide)	BCCs and SCCs	Cure rates similar to those achieved with ED & C
Phototherapy	BCCs and SCCs	Success rates for superficial BCCs is 85%-90%, and 60% to 85% for nodular BCCs; cure rates for SCCs reported between 40% and 70%
5-FU	SCC in situ	10-year recurrence rate for superficial BCC is 21%, and 5-FU is not recommended for treatment of these tumors; no good data are available for the use of 5-FU in the treatment of invasive SCC so its use for these tumors currently is not recommended
Imiquimod	Superficial BCCs	85% clearance rate of superficial BCCs reported with topical application five times weekly for 6 weeks; data are limited for the use of imiquimod in invasive SCC
Ionizing radiation	Primary BCCs and SCCs	Cure rates comparable to those achieved with surgery (ie, > 90%); however, the long-term risk for treatment-related cancer must be considered

BCC = basal cell carcinoma; ED & C = electrodesiccation and curettage; 5-FU = 5-fluorouracil; SCC = squamous cell carcinoma

venience of returning to the office for the light exposure portion of the treatment. Complications that may be experienced are burning and irritation and allergic reactions to ALA topicals; systemic effects, such as generalized photosensitivity, may sometimes be seen with the systemic photosensitizers. With the newer systemic agents, the photosensitivity period lasts only 2 to 3 days, so the patient must avoid the sun for this time following the injection of the drug.

## 5-Fluorouracil

Topical chemotherapy with 5% 5-fluorouracil (5-FU) cream is applied twice a day for 3 weeks. Because the 10-year recurrence rate for superficial BCCs is 21%,<sup>22</sup> this modality is not recommended for such tumors. It is useful for the treatment of AK and SCC in situ (Bowen's disease).

5-FU is a field treatment, so any subclinical AKs in the treatment area will be eliminated. However, 5-FU is associated with a significant, sometimes painful inflammatory reaction and with the complications of posttreatment erythema and persistent photosensitivity.

There are no good data regarding the use of 5-FU for the treatment of invasive SCC, and, therefore, its use for these tumors is not recommended.

## Imiquimod

Immune response modifier therapy—currently, with imiquimod—represents a unique approach to the treatment of malignancy in that it works at the cellular level through the release of cytokines such as interferon and tumor necrosis factor via the activation of Toll-like receptors. Topical application of 5% imiquimod five times a week for 6 weeks yields an 85% clearance rate for superficial BCCs.<sup>23</sup> Data for imiquimod's use in invasive SCC are limited.

The main advantages of imiquimod are that it is a field therapy, that it provides a good cosmetic result, and that it is well tolerated by patients. The main disadvantages are its cost and the inflammatory reaction that is sometimes seen. Complications include transient hypopigmentation and, rarely, cytokine-release syndrome (marked by flulike symptoms for a few hours after the application of imiquimod).

## Ionizing Radiation

Ionizing radiation is a treatment that has been used since the early 1900s, although it has been employed much less often since the 1960s. The usual technique is to apply superficial x-ray treatments at various fractionated schedules, usually

over a period of 3 to 4 weeks. This is an alternative to major disfiguring surgery in older patients and is usually reserved for use in patients older than 65 years of age in whom surgery may be contraindicated—for example, because of concomitant anticoagulant therapy.

The cure rates for primary BCCs and SCCs are comparable to those achieved with surgery—that is, greater than 90%.<sup>24,25</sup> Ionizing radiation provides excellent short-term cosmetic results, is noninvasive, and can be given at various schedules, providing treatment flexibility. The disadvantages include the risk for a significant x-ray scar that may develop at around 10 years posttherapy, the need for multiple visits, the high cost of the required equipment (initial purchase cost and maintenance), and the need for a specialist to provide the treatments. The complications associated with this modality are acute radiation burns, chronic radiation dermatitis, and carcinogenesis, with the possible development of other types of cancers in that area at a later date.

## Summary

The selection of treatments for NMSCs, mainly SCCs and BCCs, depends on tumor characteristics—the size, site, and histologic type. The patient characteristics—including their preference, age, and desire for a particular cosmetic outcome—as well as the practitioner's preference and experience and the facilities that are available also must be factored into the therapeutic approach. For most situations, surgery remains the gold standard, but nonsurgical options may be preferred in selected situations. Follow-up is an important part of skin cancer management, given that these patients are at significant risk for developing additional cancers over time.

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# Judging Efficacy of Treatments for Actinic Keratosis

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Each of the therapies discussed in this supplement clearly has some advantages and some disadvantages. It is also clear that a formal study protocol is required to establish—for the US Food and Drug Administration (FDA) and for clinicians—that a product has efficacy in treating actinic keratoses (AKs). Generally, with a topical therapy, the former goal of a study was to show that elimination of 80% to 90% of AKs is achieved after a 2- to 3-month course of treatment. Today, with the FDA's newer, more rigorous standards, the proof of efficacy is 100% clearance of AKs in a target area in 40% to 50% of subjects. Thus, in addition to the traditional measures (which now are secondary end points), the new primary end point in clinical research has become complete clearance in a target area.

Ultraviolet radiation exposure over time creates what might be termed a “restless epithelium.” AKs certainly occur in that sun-damage milieu. The AK is a lesion that contains cells with specific markers for squamous cell carcinoma (SCC). The cells are not yet organized into an in situ malignancy, but AKs are analogous to an abnormal Papanicolaou smear. The entire epithelial surface is damaged and has the potential to have cells that are transformed.

These factors must be considered when evaluating the efficacy of a treatment for AKs. They are especially important to the issue of recurrence. AKs are easy to destroy, provided that the therapy reaches the site of the pathology. A patient who develops AKs at follow-up after a treatment modality has been successful in clearing individual lesions has not necessarily experienced a recurrence. Instead, such lesions usually represent new AKs in the setting of a “restless epithelium.”

## Personal Clinical Experience With Interval Therapy

The primary therapy for AKs among many dermatologists is cryosurgery, which can eliminate even hypertrophic lesions with a relatively short period of cosmetic alteration. The main disadvantage of cryosurgery is that patients become discouraged by a perceived lack of long-term progress over a number of years. Many patients whom I have treated at Wake Forest have had 20 AKs frozen at every visit—some yearly, some every 6 months, and some at more frequent inter-

vals. Some patients have been treated for 18 years. I always need to educate patients that they were not experiencing recurrent AKs but were developing new lesions as a result of their considerable sun damage. What seemed clearly to be missing from therapy was an “interval approach” to eliminate many of the evolving lesions between visits for targeted ablative treatment with cryosurgery.

Clinical trials with 0.5% 5-fluorouracil (5-FU) cream showed that a significant number of patients experienced a dramatic reduction in AKs after only 1 week of therapy—the data suggested that as many as half of the AKs present at baseline were eliminated in the first week.

**[D]ermatologists must accept that we will not always have the benefit of category I evidence-based data for every treatment regimen we use.**

Subsequent studies with imiquimod demonstrated that this agent was also effective in eliminating AKs. As a result, both of these agents have been incorporated into my practice in a program that I call “interval therapy.”

I see patients at regular intervals, according to the number of AKs they develop. Generally, patients are seen once a year if they have three or four AKs at a time, every 6 months if they have 20 or more AKs at each visit, and every 2 to 3 months if they have undergone organ transplantation and are immunosuppressed. At each visit, I remove hyperkeratotic and other visible lesions with cryosurgery, and I prescribe one of two field treatments. When I prescribe 0.5% 5-FU cream, I have patients use it for 1 week. When I prescribe imiquimod, I have patients apply it for 5 days, take a 2-day break, then apply it for another 5 days. Since instituting interval therapy, patients have had far fewer AKs at each follow-up visit. Although cryosurgery is still a cru-

cial part of the treatment regimen, the number of lesions treated with this modality is reduced, such that patients are very pleased with their progress.

My anecdotal impression is that patients have a reduction of 50% or more of AKs that require cryosurgery on their follow-up visits. In addition, patients also have reported their subjective impression that their skin feels smoother, a cosmetic side benefit resulting from the elimination of a number of early, “sandpaperlike” pre-AKs.

## Studying Combination Regimens

The data for monotherapy of AKs with the agents discussed here provide sufficient evidence to establish efficacy and safety. Unfortunately, the same level of evidence-based support is not yet available for combination therapy. There are several reasons for this.

First, combination studies are often not acceptable to the FDA. Second, a study using an agent as monotherapy requires a simple and clear design: compare the therapy with placebo and establish a statistically significant difference in the achievement of the primary therapeutic end point. A study using two therapies—for example, cryosurgery plus a topical therapy (imiquimod or 5-FU)—entails a design that looks at cryosurgery plus placebo, the topical plus placebo, cryosurgery plus the topical, and two placebos. This means that four study groups must be recruited, with sufficient sample sizes. The cost of the research is at least double what it would be for a monotherapy trial.

As a result, dermatologists are faced with the frequent frustration of a process whereby a therapy is approved by the FDA, with a regimen that is ultimately not the one that we choose to use in our clinical practices. One example of an alternative regimen is the “cycle therapy” concept developed by Salasche and colleagues<sup>1</sup> for the use of imiquimod. The purpose of this treatment/rest period approach is to minimize the side effects of therapy, enhancing both patient comfort and compliance, while maintaining efficacy.

Currently in the United States, most AKs treated by dermatologists are managed with cryosurgery. In the pivotal trials that were performed prior to the applications for FDA approval for 0.5% 5-FU

cream and imiquimod, hypertrophic AKs were excluded from study. The reason is that these lesions are less likely to respond to topical treatment because these agents cannot penetrate to the source of the pathophysiology. Cryosurgery is very effective in destroying these lesions. Regimens that combine a destructive treatment such as cryosurgery (to manage hypertrophic and other visible lesions) with a field therapy that flushes out and eliminates preclinical lesions represent an optimal way of preventing progression from AK to in situ SCC (Bowen's disease) and, ultimately, to invasive SCC. In addition, having patients use self-applied field therapy, rather than enter a passive phase between cryosurgery sessions, allows them to be active participants in their cancer prevention program.

## Conclusion

Dermatologists may manage patients with as many as an estimated 350 different diagnoses during the course of a year, and dermatologic therapies often are FDA-approved for only one or two indications.

The cost of research is high, and once a drug is approved for one indication in dermatology, cost/profit analysis often makes it difficult to prompt an effort for additional studies to seek FDA approval for new indications. For example, if a drug is approved for acne, it is unlikely that it will undergo phase III clinical studies for FDA approval for rosacea, perioral dermatitis, pseudofolliculitis barbae, and related follicular inflammatory disorders.

Consequently, dermatologists must accept that we will not always have the benefit of category I evidence-based data for every treatment regimen we use. With regard to topical therapy, we must deal with the stratum corneum barrier. We must be creative, and this includes understanding that we must consider not just applying the right molecule to manage a particular disease, but also getting that molecule to the site of the pathology. By definition, this involves penetrating the stratum corneum barrier, and often this requires the use of combination therapy.

Regarding AKs, specifically, a destructive treatment alone is not optimal

because lesions that cannot be seen—sub-clinical AKs—cannot be treated. Field treatment alone is not adequate because some AKs are hyperkeratotic and the agent cannot penetrate to the site of the disease. Combination therapy solves both of these problems.

Dermatologists are infinitely creative. Given that evidence-based, category I data will not be available immediately for each specific combination therapy regimen for AKs, it is not unlikely that dermatologists will incorporate destructive and field treatments into their practices in different ways. This shift to combination regimens is likely to occur gradually over the next 10 years. The introduction of exciting new therapeutic options offers new ways to benefit our patients. We will develop ideal regimens derived from sound, evidence-based support.

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## Mechanisms of Action

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interactions with patients give clinicians the opportunity to intervene in other high-risk activities, such as cigarette smoking, that may prove to affect the skin's immune response.

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## Efficacy of Field Therapy

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Complete clearance rates analyzed according to treatment location showed that the face clears substantially more easily than the scalp.

**Intensity of Reaction.** The intensity of subjects' reactions to imiquimod will guide the way this agent should be used therapeutically. It is very clear that AKs can be eliminated by the induction of severe irritation. However, among the few patients who had no irritation at all, an impressive percentage achieved complete clearance. The ideal is to reduce substantially the number of AKs with mild, moderate, or even no irritation.

**Appearance of Subclinical Lesions.** Also documented during the phase III studies was the emergence of subclinical AKs during treatment. As is seen with 5-FU and diclofenac treatment, application of imiquimod results in an increased AK lesion count because subclinical lesions become clinically apparent.

**Discontinuations From the Study.** Very few subjects who were using imiquimod twice a week discontinued the study because of adverse reactions. Rest periods were permitted, and more patients in the active-treatment group requested rest periods than those in the vehicle group. One reason for the low discontinuation rate may have been the opportunity for rest periods.

**Adverse Events.** The most common adverse event was application-site reaction, which occurred significantly more often in the active-treatment group. There were no significant differences between the imiquimod and vehicle groups for any other adverse events, which included fatigue, fever, flulike symptoms, myalgias, rigors, headache, and lymphadenopathy. The application-site reactions included itching, burning, pain, tenderness, induration, stinging, and bleeding. These reactions are expected—and can be avoided with appropriate rest periods.

## Conclusion

The phase III studies of imiquimod, administered twice weekly, show that this unique agent is significantly better than vehicle in both complete and partial clearance of AKs. The safety data demonstrate that imiquimod use is associated with application-site reactions and local skin reactions, but these are generally well tolerated.

In practice, the exploration of the best way to use imiquimod is just beginning. For example, Salasche and coworkers<sup>5</sup> conducted a clinical study of 33 sites in 25 patients with 5 to 20 AKs per site. Patients were instructed to use imiquimod three times a week for 4 weeks, rest for 4 weeks, then—if any AKs persisted—repeat the cycle, up to a maximum of three 8-week cycles. Complete clearance was observed in 27 of the treated sites; 15 sites cleared after the first cycle. It is likely that other regimens will be tested and used once imiquimod is approved for use in AKs and that clinicians will be able to choose an optimum regimen for an individual patient.

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Table. Phase III Study of Imiquimod in AKs: Facts at a Glance

<b>Study design</b>	Randomized, double-blind, multicenter, vehicle controlled, parallel group
<b>Dosage and duration</b>	Twice weekly applications for 16 weeks
<b>Complete clearance</b>	Achieved by a significant number of subjects in the treatment group
<b>Adverse events</b>	Application-site reactions occurred significantly more often in the active-treatment group; no significant differences were found between the imiquimod and vehicle group for any other adverse events

## Immune Response Modification: A New Paradigm for the Management of Actinic Keratoses and Nonmelanoma Skin Cancers

**CME Post-Test and Evaluation**

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There is no fee to participate in this activity. Please forward the Test Answer Sheet and Evaluation Form to:

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

- Of the more than 1 million new nonmelanoma skin cancers that occur each year in the United States, approximately \_\_\_ are squamous cell carcinomas.
  - 10%
  - 20%
  - 30%
  - 40%
- As the number of organ transplantations rise and, therefore, the number of immunosuppressed individuals increases, the number of deaths due to \_\_\_ is likely to increase.
  - Actinic keratoses
  - All nonmelanoma skin cancers
  - Metastatic basal cell carcinomas
  - Squamous cell carcinomas
- Common features shared by actinic keratosis and squamous cell carcinoma include all of the following except:
  - Cumulative ultraviolet light exposure
  - Loss of polarity and atypical nuclei in keratinocytes
  - Mutation of photooncogenes such as p53
  - The possibility of spontaneous regression
- Along with exposure to ultraviolet light, the possible cofactors for the development of nonmelanoma skin cancer proposed by Stockfleth and colleagues include dysfunction of the local immune system and:
  - Activation of the nuclear factor kappa B pathway
  - Expression of interleukin-2
  - Expression of interferon
  - The presence of human papillomavirus
- Preclinical studies in the mouse model and clinical studies have shown that all of the following statements are true concerning the immune response modifier imiquimod except:
  - Imiquimod directly activates adaptive immunity
  - Imiquimod has antitumor activity
  - Imiquimod has antiviral activity
  - Imiquimod targets innate immunity
- The main mechanism of action of 5-fluorouracil is that it:
  - Activates several pathways of innate immunity
  - Interferes with DNA synthesis by blocking conversion of deoxyuridilic acid to thymidilic acid
  - Stimulates Toll-like receptors
  - Triggers apoptosis in proliferating cells
- In patients with a significant amount of photodamage and clinically evident actinic keratoses (AKs), it has been shown that subclinical AKs and expanded clones of transformed dysplastic cells are present in the surrounding skin. This statement describes:
  - "Field cancerization"
  - Invasive squamous cell carcinoma
  - Metastasis
  - Photooncogene activation
- The actinic keratoses that are least likely to respond to field therapy are those that are:
  - Hyperkeratotic
  - In an area that is severely photodamaged
  - On the face or scalp
  - Subclinical
- During treatment with field therapies—including diclofenac, imiquimod, and 5-fluorouracil—the number of actinic keratoses:
  - Decreases during therapy, but increases within 6 months of stopping therapy ("recurrence")
  - Increases at first as subclinical lesions become clinically apparent
  - Remains stable until all signs and symptoms of inflammation resolve
  - Steadily declines over the period of therapy
- The gold standard for the treatment of both squamous cell carcinomas and basal cell carcinomas is:
  - Cryosurgery
  - Electrodesiccation and curettage
  - Mohs' micrographic surgery
  - Surgical excision with standard margins

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