

## CME RECOGNITION

This SKIN & ALLERGY NEWS supplement is recognized by the American Academy of Dermatology (AAD) for 1 hour of AAD Category 1 CME credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

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

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**Estimated time to complete this educational activity:** 1 hour

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## TARGET AUDIENCE

This educational activity has been developed for dermatologists and other health care providers involved in the care of patients who present with skin lesions that have malignant potential.

## EDUCATIONAL NEEDS

A widespread lax approach to prevention of sun-induced skin problems continues to send millions of patients to dermatologists' offices for evaluation and treatment of premalignant and malignant skin lesions. Actinic keratosis alone accounts for 47 million dermatologist office visits annually. Surgical and destructive or abrasive therapies represent the primary approach to treatment of premalignant and malignant skin lesions. Topical agents have had only a minor role in the management of these lesions, aside from topical 5-fluorouracil, which many patients find difficult to tolerate. Development of effective, better-tolerated, topical agents potentially could have a major impact on the approach to management of conditions such as actinic keratosis, lentigo maligna, and cutaneous metastatic melanoma.

## LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Recognize common skin lesions that have malignant potential.
- Describe current approaches to treatment of premalignant and malignant skin lesions.
- Understand the role of nonsurgical, nondestructive therapies.
- Appreciate the therapeutic potential of effective, well-tolerated topical agents for treatment of premalignant and malignant skin lesions.

## 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. The faculty must also disclose any discussion of investigational or unlabeled uses of products.

**Dr Chapman** has received funding for clinical grants from and is a consultant to 3M Pharmaceuticals. He discusses the unlabeled use of imiquimod for the treatment of lentigo maligna. **Dr Stashower** is a speaker, consultant, and investigator for 3M. **Dr Zachary** has received funding for clinical grants from and is a speaker for Candela Laser GmbH, Iridex Corporation, Reliant Pharmaceuticals, and Sciton, Inc. He is also a consultant to Ferndale Laboratories, Inc., and SkinMedica.



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# DERMATOLOGISTS' CASE FILES

## Managing Premalignant Skin Disorders

### Management of Actinic Keratosis and Malignant Skin Lesions

**Christopher B. Zachary, MBBS, FRCP**

Despite the availability of effective preventive measures, actinic keratosis (AK) and other premalignant and malignant skin lesions make substantial contributions to dermatologists' patient volume. A product of aging and chronic sun exposure, AK occurs in about 18% of the population<sup>1</sup> and accounts for 47 million office visits to dermatologists each year.<sup>2</sup> Given current demographic trends in the United States, the impact of AK and other sun- and age-related conditions on dermatology practice will likely continue to increase.

Estimates of a single AK lesion's propensity to progress to invasive squamous cell carcinoma range between 0.025% and 16% per year, resulting in an average of about 8%, though in my opinion this latter figure is probably a little high.<sup>3</sup> Lentigo maligna, or melanoma in situ, is a pigmented lesion that has an ill-defined risk of transformation into lentigo maligna melanoma. Estimates based on expert opinion range between 33% and 50%.<sup>4,6</sup> The only estimate based on epidemiologic analysis showed a lifetime transformation risk of 4.7% for a 45-year-old caucasian and a 2.2% lifetime risk for a 65-year-old caucasian.<sup>7</sup>

As with most types of skin cancer, AK and lentigo maligna are largely preventable. Standard recommendations for skin cancer prevention (protective clothing, limitations of sun exposure, and use of sunscreen with a high sun-protection factor) would likely prevent most cases of both conditions. Because no one can predict the out-

come of an individual lesion, every lesion warrants treatment to prevent malignant progression and the need for more costly intervention.

#### AK Treatment

Historically, the vast majority of AK lesions have been treated by destructive therapies.<sup>8</sup> Reported cure rates with cryosurgery have ranged as high as 98%.<sup>8-10</sup> However, cure rates with cryosurgery appear to depend on the adequacy of treatment time. One recent prospective, multicenter trial showed that complete response rates with cryosurgery were 39% with a freezing duration of less than 5 seconds, 69% with a freezing duration of more than 5 seconds, and 83% with a freezing duration of more than 20 seconds.<sup>10</sup>

In contrast to cryosurgery, curettage with or without electrosurgery and conventional surgical excision allow for tissue sampling to rule out cancer. However, these techniques require anesthesia and can cause keloid formation.<sup>11</sup>

Dermabrasion, chemical peels, and laser resurfacing offer alternative treatment modalities but are used less frequently than simple destruction techniques. Topical therapy may appeal to patients who have numerous lesions. Historically, topical 5-fluorouracil (5-FU) has been the standard of care for diffuse AK. The agent is simple to use, effective, and inexpensive for treatment of multiple, diffuse, or microscopic lesions. However, many patients have difficulty tolerating typical

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Please go to [www.managingactinickeratoses.com](http://www.managingactinickeratoses.com)  
for more information on the treatment of actinic keratoses.

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**Management of Actinic Keratosis**

**Mitchell E. Stashower, MD**

**A**ctinic keratosis (AK) is one of the most common reasons for patient visits to dermatologists' offices. Cryosurgery, curettage and electrocautery, and conventional excision are the typical therapeutic approaches for patients with few or isolated lesions.

Topical 5-fluorouracil (5-FU) has been the standard of care for patients with diffuse AKs. The agent is easy to apply, effective, and inexpensive. However, many patients find the



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adverse effects difficult to tolerate, and long-term disease control does not match what can be achieved with surgical techniques.

Recently, imiquimod 5% cream, a topical immune modifier, was approved for treatment of AK. The agent produces a rapid and robust response that leads to clearance of lesions in a high proportion of patients. Most patients find imiquimod easier to tolerate than topical 5-FU. Long-term follow-up, although some-

what limited at this point, has been encouraging with respect to the risk of recurrence.

**Case Report**

The following case illustrates the clinical experience with imiquimod. The patient is a 74-year-old man with recurrent AKs on his face. He had been treated with 5-FU about 5 years previously and refused to undergo retreatment with the agent, and the diffuse nature of the lesions made surgical treatment problematic. He agreed to a trial of topical imiquimod. The treatment led to clearance of the recurrent lesions, and 3 years after treatment, the patient remains free of lesions.

**Figure. A 74-Year-Old Man With Recurrent AKs on His Face**



This series of images illustrates the clinical course of a typical patient with actinic keratosis treated with imiquimod. Left to right:

- 1 At presentation, the patient had diffuse subclinical AK lesions on his face and nose.
- 2 The patient began treatment with imiquimod 5% cream three times weekly, which produced a strong inflammatory reaction by 4 weeks.
- 3 After 4 months, the patient had a single residual lesion on his nose.
- 4 Patient's nose was treated with liquid nitrogen.
- 5 One year after treatment with topical imiquimod, the patient's face was clear of AK lesions.

AK=Actinic keratosis.

## Challenges of Lentigo Maligna

M. Shane Chapman, MD

The following cases illustrate the clinical difficulties posed by lentigo maligna, or melanoma in situ. Currently approved for treatment of basal cell carcinoma, imiquimod has demonstrated potential as an alternative therapy for patients who refuse surgery or who are not good surgical candidates.



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### Case Reports

One of the most comprehensive reports appeared in the *British Journal of Dermatology*. Naylor et al reported their experience with 30 patients with lentigo maligna who received open-label imiquimod daily for 12 weeks, followed by biopsies in four different areas at the end of treatment. The

As recently as 4 years ago, virtually no literature existed on the use of this topical agent for treatment of lentigo maligna. As more dermatologists have had clinical success with selected patients, case reports and clinical series have begun to appear in the medical literature. Since 2000, more than a dozen reports have been published in a variety of dermatology journals.

authors reported that 28 patients completed treatment, and 26 of 28 (93%) had complete clearance of their lesions.<sup>1</sup>

At Dartmouth-Hitchcock Medical Center, 45 to 50 patients with lentigo maligna have been treated with imiquimod. The patients comprise several common clinical scenarios: poor surgical

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Figure 1. Lentigo Maligna



This series of images illustrates the clinical course of a typical patient with lentigo maligna treated with imiquimod. Left to right:

- 1 Presentation with a typical lesion.
- 2 The beginnings of an inflammatory response early in the course of treatment.
- 3 A robust inflammatory response, a favorable observation.
- 4 Complete lesion clearance at the end of therapy.

## Topical Therapy for Cutaneous Metastatic Melanoma

M. Shane Chapman, MD

Patients who present with melanoma with metastases limited to the skin (no nodal or distant involvement) pose a challenge to dermatologists and oncologists alike. Extensive or repeated surgical treatment can lead to substantial morbidity with no promise of a cure.

Limited clinical experience with topical imiquimod has pro-

duced encouraging results in patients with cutaneous metastatic melanoma who have refused surgery (usually after one or more procedures to remove lesions) or who are not good surgical candidates. The following cases illustrate the anticancer activity demonstrated by imiquimod, which is not currently approved for treatment of metastatic melanoma. ■

Figure 1. Metastatic Melanoma



A 36-year-old male patient presented with diffuse melanoma metastatic to the skin with no nodal involvement. He had more than 250 lesions on his chest, back, one arm, and groin. He had a history of multiple cutaneous excisions, radiation therapy, and chemotherapy, none of which had cleared his lesions or prevented recurrences. Treatment with imiquimod elicited a prompt and robust inflammatory response that led to crusting and eventual clearing of all lesions over the course of 3 to 4 months. During 3 years of follow-up since the end of treatment, the patient has had no recurrences and has resumed all normal activities, which had been curtailed by skin contraction secondary to prior excisions.

Figure 2. Metastatic Melanoma

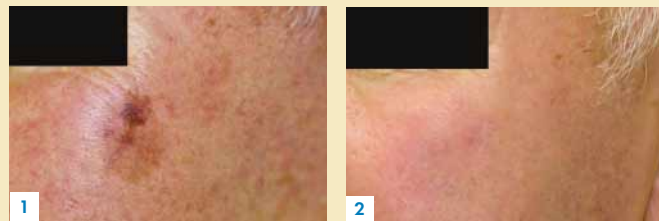


An 88-year-old woman presented with an ulcerated melanoma nodule that initially was mistaken for a diabetic foot ulcer and treated surgically. The melanoma extended to a Breslow depth of 7mm in the sole of the foot and had in situ melanoma on the periphery of the nodule. The nodule was excised and closed with a graft, but the patient refused lymph node biopsy, interferon therapy, and any further surgery to the in situ component. She agreed to treatment of the in situ melanoma with imiquimod 5% cream, which induced regression of the in situ component. The patient has regained and maintained mobility and has good functionality for her age. Whether imiquimod results in a cure remains to be seen, but the treatment clearly has had a favorable impact on the patient's quality of life.

## Challenges of Lentigo Maligna

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**Figure 2. Lentigo Maligna (Melanoma in situ)**



This patient presented with a typical lentigo maligna lesion on the upper face near the eye (left photo). After 12 weeks of treatment with few rest days, the lesion had completely cleared (right photo). More than 2 years after treatment, the patient remains disease free.

candidates, large facial lesions, recurrent disease, patients who decline surgery, patients who have had loss of function because of the disease or treatment, or lesions that have difficult margins characterized by atypical melanocytes at the periphery. The patients, some of whom remain on therapy, receive imiquimod 5 days a week for 12 weeks, with weeks ends off.

Most of the patients who have finished the entire course of

treatment have had complete clearance of lesions. Only one of these patients has had a recurrence during the last 4 years of follow-up. More definitive proof of efficacy will come with 5- and 10-year follow-up. ■

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## Management of Actinic Keratosis and Malignant Skin Lesions

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adverse effects that include pain, pruritus, burning, inflammation, erythema, and erosions. Patients must avoid sunlight during treatment with topical 5-FU. They also must take care when applying the medication near the eyes, nose, and mouth. Topical 5-FU can worsen rosacea and acne, and allergic reactions to the active ingredient or vehicle can occur.<sup>12</sup>

Imiquimod, a topical immune response modifier, has approval from the Food and Drug Administration for treatment of AK, superficial basal cell carcinoma, and condylomata acuminata. The medication works by stimulating the patient's immune system to produce  $\alpha$ -interferon, tumor necrosis factor- $\alpha$ , and interleukin-12, which in turn may induce a cytotoxic T-cell response.<sup>13,14</sup>

In two phase III vehicle-controlled studies, imiquimod reduced lesion counts by 86.6% compared to 14.3% in the control groups. Complete clearance occurred in 48.3% of imiquimod patients versus 7.2% of vehicle-treated patients.<sup>14</sup>

Other potential options for topical treatment of AK include diclofenac, tretinoin, adapalene, and tazarotene. These agents

have demonstrated varying degrees of efficacy, and tretinoin, in particular, has been suggested as a potential prophylactic therapy.<sup>8</sup>

Photodynamic therapy has proven particularly useful for patients who have multiple or diffuse lesions. Complete response rates after a single treatment session exceed 75%.<sup>12</sup>

### Lentigo Maligna Treatment

Surgery offers the most definitive form of therapy for lentigo maligna. Despite the problems of recognizing atypical melanocytes on frozen sections, Mohs techniques are often favored by dermatologic surgeons who try to optimize the competing goals of maximal lesion removal and maximal preservation of normal skin. Several variations on Mohs technique have resulted in 5-year disease-free rates approaching 100%.<sup>15</sup>

Destructive methods of treatment, including electrodesiccation and curettage and laser, have several disadvantages for treatment of lentigo maligna and, therefore, are used infrequently. The techniques usually achieve only superficial tissue removal and do not provide adequate treatment of deeper

periadnexal melanocytes, which can migrate back to the epidermal surface and cause recurrence.<sup>16,17</sup> Moreover, destructive techniques do not permit tissue sampling for pathological analysis.

Cryotherapy might be considered for patients who refuse surgery or who are not good surgical candidates. However, no efficacy data have been reported for this approach to treatment of lentigo maligna. Radiation therapy might have value as adjuvant treatment of high-risk disease or for metastatic lentigo maligna melanoma, but is not considered first-line treatment.<sup>15</sup> ■

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