Managing Premalignant Skin Disorders

Management of Actinic Keratosis and Malignant Skin Lesions

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Despite the availability of effective preventive measures, actinic keratosis (AK) and other premalignant and malignant skin lesions may have malignant potential. The only estimate based on epidemiologic 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. Lentigo maligna melanoma, or melanoma in situ, is a pigmented lesion 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. Lentigo maligna, or melanoma in situ, is a pigmented lesion with malignant potential. Estimates based on expert opinion range between 33% and 50%.4

The only estimate based on epidemiological 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.7

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 outcome 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.7 Reported cure rates with cryosurgery have ranged as high as 98%.8 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.9

In contrast to cryosurgery, curettage with or without electrocautery and conventional surgical excision allow for tissue sampling to rule out cancer. However, these techniques require anesthesia and can cause keloid formation.10

Dermabrasion, chemical peels, and laser resurfacing offer alternative treatment modalities but are used less frequently than simple destructive therapies. 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 for more information on the treatment of actinic keratoses.

CME post-test and evaluation can be accessed online at www.sdefderm.com (AAD Course No. 472-100).
A
tinic keratosis (AK) is one of the
most common reasons for patient visits
to dermatologists’ offices. Cryosurgery,
curettage and electrocautery, and con-
tventional excision are the typical therapeu-
tic approaches for patients with few or
isolated lesions.

Topical 5-fluoro-
uracil (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
adverse effects diffi-
cult to tolerate, and long-term disease
control does not match what can be
achieved with surgical
techniques.

Recently, imi-
quimod 5% cream, a
topical immune modi-
fier, was approved
for treatment of AK.
The agent produces
a rapid and robust re-
sponse that leads to
clearance of lesions
in a high proportion
of patients. Most pa-
tients 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 imi-
quimod. The patient is a 74-
year-old man with recurrent AKs
on his face. He had been treated
with 5-FU about 5 years previ-
ously and refused to undergo
retreatment with the agent, and
the diffuse nature of the lesions
made surgical treatment prob-
lematic. He agreed to a trial of
topical imiquimod. The treat-
ment led to clearance of the re-
current lesions, and 3 years after
treatment, the patient remains
free of lesions.

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.

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.

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

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 options to substantial morbidity with no promise of a cure.

Limited clinical experience with topical imiquimod has produced 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 antitumor activity demonstrated by imiquimod, which is currently approved for treatment of cutaneous melanoma.

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 produced 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 antitumor activity demonstrated by imiquimod, which is currently approved for treatment of cutaneous 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.

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adverse effects that include pain, pruriitis, 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.13

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 α-interferon, tumor necrosis factor-α, and interleukin-12, which in turn may induce a cytotoxic T-cell response.33,34

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.35

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.4

Photodynamic therapy has proven particularly useful for patients who have multiple or diffuse lesions. Complete response rates after a single treatment session exceed 75%.14

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%.15

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 periannexal melanocytes, which can migrate back to the epidermal surface and cause recurrence.36,37 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.15

References