Anticipate Hyperpigmentation in Dark Skin Acne

Therapies such as retinoids and benzoyl peroxide may trigger irritation and cause the skin to darken.

BY MICHELE G. SULLIVAN

FROM THE AMERICAN ACADEMY OF DERMATOLOGY'S ACADEMY 2010 MEETING

CHICAGO – Patient education is just as important as clinical therapy when treating acne in skin of color.

Even the best acne treatments can cause post-inflammatory hyperpigmentation in dark skin, Dr. Heather Woolery-Lloyd said.

"I always tell patients that these medications can be a little irritating and if you feel too dry or irritated, go to every other day or discontinue its use and try something else, because they can develop hyperpigmentation if the irritation continues," said Dr. Woolery-Lloyd, director of ethnic skin care at the Baumann Cosmetic and Research Institute, Miami.

Black patients have about a 29% incidence of acne – a very common cause of hyperpigmentation. "The hyperpigmented acne macule is very common," she said. "But, in black skin, comedonal lesions also show significant histologic signs of inflammation. So, if you are treating acne in skin of color, you're also going to be treating hyperpigmentation."

Because of this tendency, physicians should help patients understand the potential risks, as well as the benefits, of acne therapies. For example, she said, "About 5% of the population is sensitive to benzoyl peroxide. Black patients who are sensitive can develop an irritation that results in hyperpigmentation."

Retinoids can cause the same problem. "Some [physicans] avoid retinoids in dark skin, but I don't. I educate my patients; they should decrease the frequency of use to three times a week if irritation develops. If they do have hyperpigmentation associated with retinoids, it's going to come on very suddenly but also it typically resolves after the agent is discontinued."

Tretinoin and tazarotene are the most likely culprits, she said; adapalene is less likely to cause hyperpigmentation.

Minocycline can also cause an overall darkening of the skin. "I recently saw a patient with darkening of the lips, and have also seen reports of darkening of scars and lesions of the legs," Dr. Woolery-Lloyd said. "For this reason, I don't use minocycline as my first line of antibiotic therapy."

If you treat a lot of acne in skin of color, you'll also use a lot of hydroquinone, for dealing with post-inflammatory hyperpigmentation, she said. The drug is available in 2% strength over the counter, 4% prescription strength and can be compounded at strengths of 6%-8%. "In my practice I use the 6%-8%. It's very important to instruct the patient to apply it only to the affected area and to avoid long-term use. I don't go longer than 2 months, and then I maintain results with a different therapy."

Some patients – particularly blacks from South Africa – can develop ochronosis, a paradoxical darkening of skin associated with long-term hydroquinone use, she said. "It always starts with erythema, so again, tell your patients to discontinue if they have any irritation." After erythema, ochronosis manifests blue-black patches that can contain milia, papules, and nodules. "Histologically, you see a classic banana-shaped, ocher-colored pigment in the dermis, which can be surrounded by a granulomatous response."

Although 60% of her patients are

black, Dr. Woolery-Lloyd said she only sees one or two cases of ochronosis each year. "It's typically seen in patients who have been using over-the-counter hydroquinone every day for 20-30 years, without sunscreen," she said. "You have to emphasize to them to stop using it immediately."

A small subset of patients will have an allergic reaction when using hydroquinone – typically to the sodium metabisulfite preservative in the cream. "If they continue use, the irritation can cause a very severe hyperpigmentation," she added.

A tip for applying hydroquinone is to carefully treat only the hyperpigmented area – and not by applying the cream with a fingertip. If rubbed around, the cream can cause a halo-type affect of circular lightening. "I tell [patients] to use just a small amount and apply it with a cotton swab right on the lesion. And if they apply their retinoid over top of that, it will help to disperse it."

Dr. Woolery-Lloyd has received research funding and honoraria from Allergen, which manufactures tazarotene, and is on the advisory board and has received honoraria from Galderma, which manufactures adapalene.

Topical, Oral Agents Show Promise as Skin Cancer Defense

BY MICHELE G. SULLIVAN

FROM THE AMERICAN ACADEMY OF DERMATOLOGY'S ACADEMY 2010 MEETING

CHICAGO – In the not-too-distant future, dermatologists may be sending patients to the beach with a bagful of chemoprevention tricks to outwit ultraviolet radiation and reduce the risk of sun-related skin cancers.

"In addition to sunscreen, we'll be using these chemopreventive agents not only to reduce histologic response to ultraviolet light, but to repair the DNA damage that occurs as a result of overexposure to the sun," said Dr. Craig Elmets. "Instead of sending patients to the beach covered up with long pants, long sleeves, and a hat, we can send them off to engage in their normal behavior with less worry about the long-term consequences."

Sunscreens remain the first line of defense against cancer-inducing ultraviolet radiation, but they need backup, said Dr. Elmets, professor and chair of the department of dermatology and director of the Skin Disease Research Center at the University of Alabama, Birmingham. "They are greasy and messy, and people don't really enjoy applying them. And most people don't use nearly enough to achieve the sun protection factor stated on the label; in fact, studies show that most people only use about 25% of the necessary amount." Sunscreens also have limited effect, he said. "Over a 5-year period, sunscreens will

reduce squamous cell carcinomas by about 35%, but they have very little effect on basal cell carcinoma."

A number of agents being investigated for **a res** the chemoprevention of skin cancers have shown promising results in both animal

and human studies. Dimericine is a form of the bacterial enzyme T4 endonu-

clease. When encapsulated in a liposome and applied topically, the compound appears to boost the body's DNA repair response by increasing base excision repair, Dr. Elmets said.

A 2001 study allocated 30 patients with xeroderma pigmentosum to dimericine or placebo for 1 year, in addition to sunscreen. Patients in the active group had a 68% reduction in actinic keratoses and a 30% reduction in basal cell carcinoma (Lancet 2001;24:926-9).

Dr. Elmets is the lead investigator in one of two ongoing dimericine trials. The first is a phase II study randomizing kidney transplant patients with nonmelanoma skin cancer to the drug or placebo for 12 months, with an outcome of new nonmelanoma skin cancers. The second, a phase III study, aims to recruit up to 30 patients with

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> xeroderma pigmentosum who will be allocated to dimericine or placebo, with the primary end point of new actinic keratoses.

> "Another exciting molecule that may have good chemopreventive potential is GDC-0449," Dr. Elmets said. The compound is a systemic hedgehog pathway antagonist. "The hedgehog pathway is an important regulator of cell growth and differentiation during embryogenesis. But mutations are associated with basal cell carcinomas in both children and adults," he said. Animal research has shown that inhibiting this pathway can reduce tumor growth.

> In a study of 33 patients with metastatic or locally advanced basal cell carcinoma who took the drug at different doses, 18 achieved a response; 2 were

complete and 16 were partial. Disease stabilized in 15 patients and progressed in 4 (N. Engl. J. Med. 2009;361:1164-72).

Twenty-four trials, in progress or recruiting, focus on GDC-0449's safety and efficacy in a va-

riety of cancers, including basal cell nevus syndrome, and pancreatic, gastrointestinal, lung, breast, and brain cancers.

DMFO (alpha-difluoromethylornithine, also known

as effornithine) irreversibly inhibits ornithine decarboxylase, an enzyme unregulated in many tumors. In a recent phase III trial of 219 patients with a history of nonmelanoma skin cancer. there was no significant difference in the total numbers of nonmelanoma skin cancers between the active and placebo group after 4-5 years of followup (more than 1,200 personyears). But new basal cell carcinomas were 33% less common in the active group than in the placebo group (Cancer Prev. Res. 2010;3:35-47).

There are 20 active or completed trials looking at this agent in relation to several cancers, including bladder, GI, neuroblastoma, and trypanosomosis.

The cyclooxygenase-2 inhibitor celecoxib is also in the skin can-

cer race. "COX-2 is dramatically upregulated in actinic keratoses and squamous cell carcinomas, and also in the interstitial space around basal carcinoma tumor islands," Dr. Elmets said. "When given orally, it inhibits COX-2 expression, reducing the prostaglandin E2 production implicated in skin cancers."

A recent study of 60 patients with basal cell nevus syndrome treated with celecoxib found that those with less severe disease had a 20% increase in the number of basal cell carcinomas over 24 months, compared with a 50% increase in those taking placebo (Cancer Prev. Res. 2010;3:25-34).

Finally, Dr. Elmets said, an ancient and familiar drink holds intriguing possibilities. The primary catechin in green tea, EGCG, (epigallocatechin-3-gallate) is a potent antioxidant that appears to reduce histologic and clinical damage from exposure to ultraviolet lights A and B. "When ECGC is applied topically or given to animals to drink in their water, they show a dramatic reduction in new skin cancers. In humans, it reduces UVA and UVB erythema," he said.

Dr. Elmets disclosed that he has received research support from Pfizer Inc. and holds an intellectual property right on the use of EGCG as a skin cancer chemopreventive agent.