Clinical Insights on Skin Cancer in Immunosuppressed Patients

Specialists offer strategies for dealing with two potentially challenging instances of skin cancer.

By Paul Winnington, Editor-in-Chief
As rates of melanoma and non-melanoma skin cancer continue to climb, dermatologists face the increased likelihood of managing patients in unique circumstances. A particular challenge may be managing skin cancer in an immunocompromised patient. By reviewing the approach to two distinct patient groups, dermatologists may uncover specific management strategies as well as more general guidelines for patient care. Below, specialists discuss medical treatment of multiple non-melanoma skin cancers in an organ transplant patient and counseling regarding melanoma during the relative immunosuppression of pregnancy.

**Oral Retinoids for NMSC Suppression**

As reports of successful use of oral retinoids to suppress the development of non-melanoma skin cancer (NMSC) continue to emerge, use of these agents to prevent cutaneous malignancies in appropriate patient populations may expand. Many clinicians recognize the potential benefit of oral retinoids in management of NMSC but seek advice about patient selection and dosing.

Speaking at the American Academy of Dermatology's Academy '06 meeting this summer, Mark Lebwohl, MD, Sol and Clara Kest Professor and Chair of the Department of Dermatology at Mount Sinai School of Medicine, observed that ample evidence supports the chemopreventive activity of oral retinoids in NMSC and offered insight on their use.

Some data regarding oral retinoids and skin cancer comes from studies of psoriasis patients with a history of phototherapy and/or cyclosporine use. Patient history of PUVA phototherapy is associated with risk of developing NMSC, particularly SCC. Data also support an association between cyclosporine therapy and an increased risk of NMSC. One study confirmed that cyclosporine use increased the occurrence of PUVA-induced skin cancers, but found that acitretin decreased occurrence of SCC in patients with a history of long-term PUVA therapy.

Data from xeroderma pigmentosum patients also show a chemopreventive action for oral retinoids, Dr. Lebwohl noted. One study documented a significant decrease in the development of BCCs and SCCs in five XP patients treated with oral isotretinoin 2mg/kg daily. Two studies demonstrated tumor suppression among XP patients treated with etretinate (of which acitretin is a metabolite). The addition of topical imiquimod 5% cream three times weekly to a regimen of oral acitretin (20mg daily) reportedly produced tumor clearance at six-months for one teenage XP patient initially diagnosed with multiple BCCs. Studies also support chemopreventive effects of etretinate in nevoid basal cell carcinoma syndrome.

Given the known risk of NMSC in both heart and kidney transplant patients, attention has focused on oral retinoid therapy to confer chemopreventive benefits against skin cancer development in this population. Dr. Lebwohl reports that, based on studies, the risk of SCC is about 65-times higher in transplant patients than in the general population, while the risk of BCC is about 10-times that of the general population. Furthermore, transplant patients are at increased risk for metastasis and death from SCC, while BCC in transplant patients may be more aggressive and associated with a higher degree of morbidity and mortality.

Given these risks, it's obvious that clinicians would welcome a safe and effective intervention to help suppress NMSC in this population. Multiple studies support the use of oral retinoids for chemoprevention, Dr. Lebwohl said. Specifically, acitretin has been linked with significantly decreased rates of SCC development, decreased number of BCCs, and reductions in the incidence of or thickness of AKs. Oral isotretinoin has also been associated with NMSC suppression, particularly decreased incidence of SCC.

**Systemic Therapy Guidelines.** Oral retinoid therapy may be an ideal option for chemosuppression of NMSC in two instances, Dr. Lebwohl observes:

1.) patients who present with multiple NMSCs and have co-existent psoriasis
2.) patients who are immunosuppressed, particularly transplant patients, and develop multiple NMSC.

Additional indications for use of systemic retinoids may include development of multiple skin cancers (more than five to 10) per year and acutely increased frequency of SCC formation.

Photoprotection is the foundation of the approach to the patient with multiple NMSC, Dr. Lebwohl notes. Treatment of specific AKs is indicated, using the modality of the physician's choice (imiquimod, diclofenac, 5FU, photodynamic therapy, cryotherapy, TCA peels, etc.) based on the presentation and appropriate patient input.

The dermatologist should consult with the patient's other physicians to discuss any appropriate methods to reduce immunosuppression. Next, treatment of specific non-melanoma skin cancers by appropriate modality (Mohs surgery, ED&C, imiquimod, etc.) is indicated.

Finally, the dermatologist may initiate long-term, low-dose oral retinoids in appropriate patients.

**Acitretin-Specific Considerations.** Drawbacks of acitretin therapy for management of NMSC are similar to those for any other indication. Most common complaints are dry lips, dry mouth, and hair loss. However, Dr. Lebwohl notes, there have been no reports of detrimental effects on renal function.
Current recommendations call for 25mg acitretin per day or every other day, depending on patient tolerance. If patients can tolerate it, therapy may be initiated at the 25mg daily dose, Dr. Lebwohl says. Alternatively, a dose-escalation scheme has been proposed, initiating therapy at 10mg/day, increasing to 20mg/day after two to four weeks, then to 25mg/day after another two-to-four week interval.

All patients treated with acitretin must not donate blood products during therapy and for three years following discontinuation of therapy. Prior to initiation of therapy with acitretin, all patients should undergo lipid and liver function tests. These should be repeated every two to four weeks for two to three months or until liver function and lipid levels are stable. Tests should be repeated at three-month intervals and following each dose increase. If treatment is necessary to manage lipid levels, Dr. Lebwohl recommends use of gemfibrozil (Lopid).

Women who are pregnant or who may become pregnant must not use acitretin. Among women of child-bearing age, Dr. Lebwohl recommends using acitretin only in those severely affected by NMSC who are unresponsive to other therapies or in whom no other therapy may be used. Obtain two negative pregnancy tests prior to initiating therapy, and require two forms of contraception for at least one month prior to the initiation of therapy and for at least three years after discontinuation of therapy. Microdosed progestin-containing oral contraceptives are not appropriate.

Although it is also teratogenic, isotretinoin has a shorter-half-life and may be a better choice for women of child-bearing potential who meet the criteria for chemopreventive therapy, Dr. Lebwohl notes. All appropriate screening, monitoring, and registration protocols must be followed.

Since ethanol increases the half-life or acitretin, alcohol consumption has been widely discouraged among patients being treated with acitretin. However, since the increased half-life extends the duration of teratogenic potential, it is only a concern for women of childbearing potential, Dr. Lebwohl points out. Women of childbearing potential must not consume alcohol while undergoing acitretin therapy. Alcohol consumption by other patients is not problematic.

Considerations Regarding Sirolimus. Sirolimus (Rapamycin) is a newer anti-rejection therapy that demonstrates activity against cutaneous cancers. It is not a retinoid but warrants mention because rates of SCC development are significantly lower in sirolimus-treated renal transplant patients compared to cyclosporine-treated patients. Dr. Lebwohl reported that in studies, patients receiving sirolimus plus cyclosporine had lower rates of SCC compared to those receiving cyclosporine plus placebo. Among patients receiving combination sirolimus plus cyclosporine, a group in which cyclosporine was withdrawn developed fewer SCCs than did those who remained on the two-agent regimen. Sirolimus may warrant consideration in order to reduce immunosuppression and NMSC risk in certain high-risk transplant patients.

Counseling Melanoma Patients About Pregnancy

Estimates suggest that about one-third of women diagnosed with cutaneous melanoma are of child-bearing age at the time of diagnosis, noted Jean Bolognia, MD, Professor of Dermatology at Yale University School of Medicine, when speaking about management of melanoma in pregnancy at Academy ‘06. Recommendations from the middle of the last century—disproven in the past 25 years—have contributed to some confusion regarding the relationship between pregnancy and melanoma. Since dermatologists may find themselves counseling women who have had melanoma or actively managing melanoma in a pregnant woman, they must be prepared to accurately and effectively address a number of issues. Dr. Bolognia identified five questions related to melanoma and pregnancy and offered guidelines for responding appropriately.

Should a woman previously diagnosed with melanoma get pregnant? Although some researchers in the 1950s proposed that women diagnosed with melanoma should be counseled to avoid pregnancy and/or to consider sterilization, subsequent research refutes those conclusions, Dr. Bolognia said. Nonetheless, patients may seek advice from dermatologists prior to becoming pregnant. Data from controlled trials reveal that subsequent pregnancies had no effect on the dis-
ease-free interval or on overall survival in women who became pregnant within five years of melanoma diagnosis.\textsuperscript{11,12} (This data excludes women who presented with recurrent melanoma within two years of initial diagnosis). Therefore, Dr. Bolognia concluded, there is no evidence to suggest that women who have been diagnosed with cutaneous melanoma and successfully treated must avoid pregnancy for their lifetime. However, an appropriate waiting period is indicated.

**How long must a woman treated for melanoma wait before becoming pregnant?** Because there is no evidence that pregnancy negatively influences disease-free interval or survival, the primary objective in delaying pregnancy is to help ensure that a woman postpones pregnancy until a time when she is at minimal risk for recurrence or metastasis. As Dr. Bolognia puts it, “You want to be sure you will be there for the child.”

Based on the data, including findings that most recurrence of melanoma will occur within three years of initial diagnosis\textsuperscript{13} and that approximately 80 percent of patients with metastatic disease present within two years of initial diagnosis,\textsuperscript{12} in general Dr. Bolognia recommends a two-year delay before becoming pregnant (unless the patient has high-risk disease in which a three-year delay is recommended).

However, this recommendation may need to be individualized. For example, a 40-year-old woman with an in situ melanoma may not need to wait for any period of time before attempting to become pregnant.

**What is the prognosis if diagnosed with melanoma while pregnant?** Receiving a diagnosis of melanoma during pregnancy can be especially difficult for a patient. Pregnancy tends to be an emotionally-charged period, Dr. Bolognia noted, and patients are often susceptible to conflicting advice from friends, family, Ob/GYNs, and other physicians. In multiple studies of localized cutaneous melanoma, when researchers controlled for Breslow depth, they found that pregnancy had no effect on prognosis for a woman with melanoma, Dr. Bolognia observed. Pregnant women diagnosed with stage I/II melanoma have a similar prognosis to age-matched controls, she said. For more advanced stage disease, pregnancy itself may influence disease progression and treatment, thereby affecting long-term prognosis.

**What can dermatologists do to minimize depth of melanomas identified in pregnant women?** One troublesome finding regarding melanoma diagnosed during pregnancy, Dr. Bolognia noted, is that in a few studies melanomas diagnosed in pregnant women tended to be thicker than those diagnosed in other women. The reasons for this are unclear, though Dr. Bolognia suggests a few possible contributing factors.

Importantly, she said, dermatologists must abandon the myth that “moles change during pregnancy.” Obviously, moles on the abdomen or in areas of significant weight gain may change in appearance, however data do not support the notion that nevi change in size during pregnancy.\textsuperscript{14} In fact, Dr. Bolognia said dermatologists should lower their threshold for performing a biopsy of suspicious pigmented lesions in pregnant women.

Additionally, Dr. Bolognia said, the relative immunosuppression of pregnancy could theoretically contribute to increased lesion thickness, as may the combined effect of hormones and placental growth factors present in the milieu of pregnancy.

**What is the relationship between estrogen and melanoma?** According to Dr. Bolognia, earlier research suggested that the melanoma cells expressed estrogen receptors. This finding contributed in part to the previously-held belief that pregnancy (and its associated high estrogen levels) as well as the use of hormonal contraceptives posed a risk to women with a history of melanoma. However, subsequent research utilizing more specific monoclonal antibodies failed to detect estrogen receptors on cutaneous melanomas, including melanomas diagnosed during pregnancy. Oral contraceptive pills are appropriate for use by women with a history of melanoma, Dr. Bolognia said.

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