**CASE STUDY**

**A 36-YEAR-OLD TRANSPLANT RECIPIENT WITH ACTINIC KERATOSIS**

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**BACKGROUND**

KH is a 36-year-old, white female with blonde hair and hazel eyes. In 1998, she had a double organ (pancreas and kidney) transplant because of uncontrolled diabetes. Since then, she has been treated for basal cell carcinoma (BCC), moderate acne rosacea, herpes simplex virus (type 1), and actinic keratoses (AK). In 2004, she received photodynamic therapy with aminolevulinic acid for multiple facial AKs. Within 24 hours, she experienced a severe phototoxic reaction, including moderate-to-severe erythema of the face after minimal sun exposure. She was empirically treated with famciclovir and prescribed pain medication and aluminum sulfate soaks. At follow-up, her skin was found to have healed well, and the AKs were resolved. Within 2 weeks of the reaction, she was able to tolerate application of sunscreen and tretinoin. In 2005, she was treated with twice-daily imiquimod 5% cream after a surgical biopsy for superficial and nodular BCC of the left side of the chest. When she reported extreme erythema, edema, and crusting, in addition to intermittent pruritus and stinging during treatment, the frequency of treatment was decreased intermittently. No blister was noted.

At her biannual full-cutaneous examination (FCE), she reported a persistent scaly growth on the upper right side of the chest that she first noticed after a vacation at the beach 2 months ago. During FCE, a thin, eryhematosus plaque 6 mm by 5 mm in size with fine scale, suggestive of AK, was visible on the right subclavicular region. A prominent nevi pattern was noted and included 10 nevi of 5 mm or more in size and more than 50 nevi of 10 mm or more in size. No findings were suggestive of malignant melanoma (MM), squamous cell carcinoma (SCC), or BCC. Furthermore, there were no signs of recurrence at the previous sites of BCC, and no new or recurring AKs on the face were noted. Her medications included immunosuppressants (ie, mycophenolate mofetil, cyclosporine, and prednisone), in addition to oral calcitriol, trimethoprim/sulfamethoxazole, tretinoin cream, and clindamycin lotion.

**TREATMENT PLAN**

Treatment with once-daily imiquimod 5% cream 3 times weekly for 12 weeks was initiated. A topical therapy was chosen after the patient rejected cryotherapy or surgical excision because of the risk of permanent hypopigmentation or scarring. Imiquimod 5% cream effectively cleared the patient’s previous BCC without complication, and she tolerated it well; therefore, the nurse practitioner (NP) decided to use this medication again.

The risks, benefits, and expected results of imiquimod therapy were reviewed with the patient. She was told “red is good” and is generally a sign of an immune response, but “pain is not” and a break in therapy is needed if the treated area becomes tender. The patient was informed that most patients experience local skin reactions including erythema; flaking, scaling, or dryness; and scabbing or crusting. If no reaction was seen within 2 weeks of initiating therapy, she was instructed to discontinue use of the medication and notify her NP. The patient was instructed to be extremely cautious about sun exposure, advised to wear protective clothing, and told to use a physical sunblock containing zinc oxide or titanium dioxide, rather than a chemical sunscreen, for optimum protection and less irritation.
OUTCOME AND FOLLOW-UP

Violent redness occurred within the first week of imiquimod application, followed by crusting. The patient tolerated the regimen well and denied having pain. However, she did report an intermittent, mild itching and a tingling sensation. Six weeks after imiquimod therapy was initiated, moderate erythema and mild crusting were noted, but no evidence of blister or ulceration was found. After a 4-month regimen of imiquimod therapy was completed, the AK completely resolved. Chemoprevention with topical tretinoin, applied to the entire neck and chest 2 to 3 times weekly, was initiated. The patient was instructed to take a break from treatment if she experienced itching, tightness, burning, discomfort, or excessive, bothersome peeling. She was told to use a physical sunblock in place of daily moisturizer.

The risks, benefits, and reasonable expectations of topical tretinoin used as a chemopreventive agent were then reviewed with the patient. She was told that tingling or slight stinging upon application, temporary increased erythema, and intermittent peeling of the skin are common side effects of topical tretinoin therapy. She was told that acne may flare after topical tretinoin therapy is initiated. However, with prolonged use of topical tretinoin, acne, enlarged oil glands, pore size, and dark spots diminish considerably. The NP explained that temporary irritation may result and last 6 to 12 weeks and that peeling indicates that repair of sun damage is occurring. KH was encouraged to take a break from treatment for 1 or 2 days if excessive irritation or peeling occurred. Most importantly, the NP emphasized the fact that the development of AK and subsequent SCCs can be halted by topical tretinoin therapy. Additionally, the patient was told to discontinue topical retinoid treatment before trying to become pregnant or if pregnancy occurs, in light of the possibility of teratogenic effects posed by tretinoin.

At the 6-month follow-up visit, no evidence of AK, BCC, SCC, or MM was found. Results of FCE were unremarkable. The patient was tolerating application of topical tretinoin to the face daily and to the neck and chest nightly 3 times weekly without difficulty. She reported utilizing a physical sunblock faithfully as a moisturizer and re-applying it when she was exposed to UV rays.

DISCUSSION

SPECIAL CONSIDERATIONS FOR TRANSPLANT RECIPIENTS

Immunocompromised persons, such as transplant recipients (TR), are at heightened risk for the development of certain cancers. Skin cancer, including SCC, melanoma, and BCC, is the most common malignancy in TRs and affects between 30% and 70% of these patients within 20 years of organ transplantation. Thus, education regarding sun exposure, close monitoring, and early treatment are critical for these patients. For a patient, such as KH, the importance of being “sun-smart,” performing monthly self cutaneous examinations, and receiving biannual FCEs at a specialized dermatologic facility must be reinforced.

MECHANISM OF ACTION AND EFFICACY OF IMIQIMOD

Unlike other treatments for AK, imiquimod is an immune-based therapy. It has been shown to stimulate the immune system by activating antigen-presenting cells to produce interferon and other chemokines and cytokines. These cytokines stimulate several other components of the innate immune response and help direct the adaptive immune response. The pathogenesis of AK involves suppression of the immune response against abnormal cells; thus, a therapeutic approach, such as imiquimod, which can reverse this immunosuppression, could potentially reduce the rate of AK recurrence and the possibility of malignant transformation.

A recent open-label uncontrolled, nonrandomized pilot study evaluated the safety and efficacy of imiquimod 5% in the treatment of AKs in 6 organ TRs. The study showed clearance of all AK lesions after 12 to 16 weeks in 5 of the 6 TRs, with the latter showing partial clearance. Local erythema, edema, and mild erosion at the site were reported; no wound infection or scarring was observed. Immunosuppressive therapy remained unchanged throughout the treatment with all graft-related laboratory parameters remaining stable during and after treatment. A randomized, double-blind, placebo-controlled trial evaluated safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal TRs. In 1 year, fewer squamous skin tumors arose in the areas treated with imiquimod compared to control. Renal function was not adversely affected. The authors concluded, “5% imiquimod cream seems to be effective on skin areas up to 60 cm² in renal TRs.” These data are encouraging for the use of topical immunomodulators...
in TRs. There has not been evidence of systemic absorption or threat of organ rejection in this high-risk population. Further studies are needed in this area to substantiate these findings.

Imiquimod 5% cream has been shown to be safe and effective for the treatment of clinical and subclinical AKs and to produce excellent cosmetic results. It has been reported to reduce baseline lesion counts by a median of 86.6% compared with a median reduction of 14.3% in patients treated with vehicle only. A meta-analysis of 5 short-term trials found 50% of patients treated with imiquimod achieved complete clearance, and 65% had partial (>75%) clearance. In contrast, among patients treated with vehicle only, 5% achieved complete clearance, and 11% had partial clearance. Long-term studies have found a low incidence of new AK in imiquimod-treated areas, which suggests that imiquimod may stimulate immune-cell memory and induce an antitumor response.

CHEMOPREVENTION

Chemoprevention is defined as oral or topical use of dietary or pharmacologic agents to inhibit or reverse the development of cancer. AK in TRs are more aggressive than AK in immunocompetent persons. Thus, TRs have a special need for a fast-acting chemopreventive treatment. Several agents, such as difluoromethylornithine, nonsteroidal anti-inflammatory drugs, and green tea and grape seed extracts, appear to be promising options for the chemoprevention of nonmelanoma skin cancer. However, to date retinol and the retinoids are the only compounds proven to be chemoprotective. No agent has yet been approved by the US Food and Drug Administration for the chemoprevention of skin cancer.

Retinoids are structural and functional analogs of vitamin A that appear to act chemopreventively by inducing growth arrest or apoptosis of tumor cells, by modulating the immune response or differentiation of keratinocytes, or by exerting some combination of these actions. Studies have shown that topical retinoids (eg, tretinoin) may reduce the number of AKs in TRs, although their effect is less dramatic than that of systemic retinoids.

REFERENCES