What do we know about immunosuppression and the risk of NMSC in transplantation patients?

The association between immunosuppression and non-melanoma skin cancer (NMSC) risk is well established. In fact, level of immunosuppression is directly related to incidence of NMSC.1,2 (Table 1) Forty percent of solid organ transplant recipients (SOTRs) experience premalignant skin tumors within the first five years of immunosuppression. Actinic keratosis (AK) and squamous cell carcinomas (SCC) are far more common in this population than basal cell carcinomas (BCCs).

Of note, premalignant and malignant lesions in SOTRs more frequently have aggressive histological subtypes and uncommon clinical morphologies as well as uncommon presentations. The mortality rate for skin cancers in the SOTR population is five to eight percent.3 As with NMSC in the general population, multiple factors, including human papilloma virus (HPV) and UVA/B exposure augment the risks.

Among renal transplant patients, there is a biphasic increase in skin cancer incidence based on age at transplantation, with a steady increase in risk for older recipients (age 50+ years), beginning at year two. Among those patients under age 50, NMSCs took longer to occur, but by six years, the skin cancer risk was 200-times greater than for age-matched non-transplanted controls.4

Male RTRs are at particular risk of invasive SCC at sun-exposed sites, such as the scalp and the external ear. Risk of malignant melanoma and Kaposi sarcoma are also increased relative to the nontransplanted population.4

One study evaluated the risk for NMSC among 100 consecutive liver transplant recipients (LTR) seen by two dermatologists, finding seven NMSCs (one SCC, six BCC) in four patients. Among the total LTR population evaluated, 35 percent were on triple-drug therapy (ciclosporin A, azathioprine and prednisolone), 48 percent were on dual therapy (tacrolimus and prednisolone), and 17 percent were on monotherapy (tacrolimus).

The authors suggest that the relatively low rate of NMSC in this study population is due to the fact that so many patients were on dual or monotherapy versus triple-
drug therapy, and there was a short overall duration of treatment.\textsuperscript{5}

Interestingly, certain immunosuppressants are associated with a reduced risk for NMSC. (Table 2) In light of this finding, it may be possible to switch high-risk patients from immunosuppressive therapies with a higher risk of NMSC to regimens associated with a lower risk. Trials underway seek to ascertain the feasibility and benefit of switching patients to sirolimus-based therapy.

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Reduced Risk</th>
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<tbody>
<tr>
<td>Cyclosporine</td>
<td>Sirolimus</td>
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<tr>
<td>Azathioprine</td>
<td>Mycophenolate mofetil</td>
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<tr>
<td>Tacrolimus</td>
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<td>Voriconazole</td>
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What about the association between HPV and SCC? Could immunomodulation aid prevention?

Several types of HPV have been associated with SCC, including HPV 5, 8, 9, 12, 14, 15, 17, 19-25, and others. Of note, 30 to 60 percent of these patients develop multiple SCCs on sun-exposed sites after 10-30 years. Moreover, HPV 5 and HPV 8 have been found in more than 90 percent of SCCs from these patients.\textsuperscript{6} Research suggests that E6 proteins bind and inactive p53 and BAK; inactivation of p53 slows DNA repair. Furthermore, the anti-apoptotic effect of E6 in HPV is thought to be a tumor-inducing factor.\textsuperscript{7} In light of these findings, there is some interest in investigating the benefits of HPV vaccination for AK and SCC.

What are the best treatments to reduce NMSC risk or treat NMSC in immunosuppressed patients?

In order to understand treatment options, it is essential to review the basic pathogenesis of UV-induced SCC, essentially a three-step progression (Figure 1). In normal cells, UV exposure can induce p53 mutation, leading to subclinical AK. Additional cumulative UV exposure can induce RAS mutation, and the formation of clinical AK. Further UV exposure leads to p16 mutation, and the progression to SCC.

Use of sunscreen and UV avoidance work to protect normal cells and thereby prevent p53 mutation. Once UV damage has been done, treatment may be targeted at arresting mutagenesis. The activity of imiquimod is most beneficial in the preclinical and clinical AK stages, modulating p53 and RAS. Topical 5FU is effective in the clinical AK stage, at the point of RAS mutation. In light of the emerging notion of field-based treatment for AKs, it may be noted that topical agents may confer some chemotherapeutic benefit by addressing preclinical lesions and abnormal cells.

Retinoids offer the broadest spectrum of activity for AKs and SCC; they appear to confer protective benefits for normal cells. Additionally, retinoids may affect both RAS mutation and p16 mutation. (Figure 1)

The efficacy of both acitretin and isotretinoin (more commonly used for nevoid basal cell carcinoma syndrome or BCNS) for the prevention of NMSC is well established in the literature,\textsuperscript{8,9,10} although some trials and case series lack rigor,\textsuperscript{8} and there is no consensus on dosage or duration of treatment.\textsuperscript{9}

**Table 2. Immunosuppressants and SCC**

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**Table 3. Considerations for Chemoprevention**

- Tumor burden
- Risk of metastasis
- Morbidity and inconvenience
- In high-risk patients, the benefits of systemic chemoprevention outweigh the adverse effects
- Augments, does not completely replace surgical therapy

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**Figure 1. The Pathogenesis of SCC and the Activity of Various Agents. Colored arrows correlate with point of activity for each agent.**
“Among renal transplant patients, there is a biphasic increase in skin cancer incidence based on age at transplantation, with a steady increase in risk for older recipients (50+ years), beginning at year two.”

What are the main strategies for systemic chemoprevention of NMSC and when should they be considered?

There are two primary systemic strategies for chemoprevention: use of oral retinoids or reduction of immunosuppression. The choice of a strategy depends on various factors.

Systemic chemoprevention may be indicated as it becomes increasingly difficult to balance the morbidity and inconvenience of surgery against its benefits. The dermatologist must also weigh the risk of progression against the risks of adverse effects of systemic therapy.

Importantly, chemoprevention does not replace or obviate the need for surgical excision of tumors. Of course, regular surveillance is essential.

Are there other options to consider for chemoprevention and protection?

There is a growing body of evidence in support of cyclic photodynamic therapy (PDT) for the treatment and prevention of AKs and SCCs in SOTRs. Photodynamic therapy sessions using 5-ALA administered at four- to eight-week intervals was shown to reduce the incidence of SCCs in a cohort of 12 high-risk SOTRs, with good tolerability of treatment. This benefit likely derives from the field effect of PDT, shown to reduce the number and increase the mean time to formation of new NMSC lesions in split-face trials.

Polypodium leucotomos is an aquatic fern originating in Central America that adapted to life on land using natural protective mechanisms against UV. The extract is obtained from selected plants and provided in a tablet form for daily use (Heliocare, Ferndale). It had been used for centuries by native Americans as an anti-inflammatory agent.

Studies of the effects of Polypodium leucotomos extract on UV-exposed skin suggest that it reduces the induction of reactive oxygen species and lipid peroxidation. Polypodium leucotomos appears to undo suppression of dendritic cell activation induced by UVR and subsequently inhibit TNF release. This activity restores the hypersensitivity response to UVR. However, there is currently no evidence to support this agent as a chemopreventive modality, as it is marketed for photoprotection.

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**TABLE 4. SURVEILLANCE OF HIGH-RISK PATIENTS**

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<tr>
<td>Early recognition and treatment are essential</td>
<td>Patients should conduct monthly self-exams</td>
<td>Regular in-office exams by the dermatologist are indicated</td>
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<tr>
<td></td>
<td></td>
<td>Intervals of one to 12 months, based on risk level (See Stasko, et al.)</td>
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<tr>
<td></td>
<td></td>
<td>Treat AKs early</td>
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<td></td>
<td></td>
<td>Maintain low level of suspicion</td>
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**PRACTICAL POINTER**

There are two primary systemic strategies for chemoprevention: use of oral retinoids or reduction of immunosuppression. The choice of a strategy depends on various factors. Systemic chemoprevention may be indicated as it becomes increasingly difficult to balance the morbidity and inconvenience of surgery against its benefits.