ABOUT THE AUTHOR

Sheila Au, MD, FRCPC

Dr. Sheila Au is a Clinical Associate Professor in the Department of Dermatology and Skin Science at the University of British Columbia. She was the Head of the St. Paul's Hospital Division of Dermatology from 2009 to 2019. She is a hospital-based medical dermatologist with a special interest in transplant-associated skin disorders, emergency dermatology, and cutaneous manifestations of rheumatic disease. She is the director of the Skin Cancer Post-Transplant Clinic (SCREEN Clinic) and co-director of the Dermatology and Rheumatology Clinic (DART Clinic) at St. Paul's Hospital in Vancouver, BC. Dr. Au received the 2019 Practitioner of the Year Award from the Dermatology Society of British Columbia.

PREVENTING SQUAMOUS CELL CARCINOMA IN THE POST-TRANSPLANT PATIENT

Skin cancer is a leading cause of mortality and morbidity in the post-renal transplant patient.[1] Squamous cell carcinoma (SCC) is the most common post-transplant malignancy (up to 250x more common than in the general population).[2] The three main pathogenetic - and synergistic - risk factors are cumulative ultraviolet light exposure, immunosuppression, and oncogenic viruses, especially human papillomavirus (HPV).[3] How else can the dermatologist impact patient care beyond chasing skin cancers at every visit? This article will focus on a few strategies utilized in the Skin Cancer Post-Renal Transplant Clinic (SCREEN Clinic) at St. Paul's Hospital in Vancouver, BC.

Triage patients

Triaging patients into low, medium and high-risk groups is recommended in the dermatologic literature[4,5] and allows the clinician to determine a) appropriate examination intervals and b) how aggressive preventative strategies need to be.

In the SCREEN clinic, anyone with a history of actinic keratoses (AK) or skin cancer is considered high-risk and is followed every two to four months depending on the rapidity of onset of skin cancers. Patients with type V or VI skin phototype are considered low-risk and are followed every two to three years. Everyone else is considered medium risk and is followed one to two times per year. This follow-up is essential. It is common for patients to jump from medium to high-risk as time post-transplant progresses, especially if other predictable risk factors are present (photodamage, low Fitzpatrick skin type, positive family history of skin cancer, tanning bed use, etc.).

Other transplant-specific risk factors for SCC that might prompt more frequent screening include male patient, Caucasian, > 50 years of age at transplant, retransplantation (more potent immunosuppression), time post-transplant (more cumulative immunosuppression), history of lymphoma or leukemia, immunosuppressive regimens containing azathioprine and cyclosporin, and the use of photosensitizing agents such as voriconazole.[1,6]

We find that keeping an easy-to-access tally of skin cancer type, date, and location in the patient's chart is invaluable. This quick reference provides an immediate visual picture of your patients' cumulative skin cancer burden, and all chemopreventative decisions are based on these numbers and timelines.

Patient assessment

At every visit, we focus on the highest risk lesions. Rapidly growing, ulcerated, or tender nodules are prioritized for biopsy. Patients are counselled that a lump that doubles in size in a month or a scab that doesn't heal is a skin cancer until proven otherwise. Some patients have dozens of keratotic lesions of seborrheic keratoses/ HPV/ papillomas/Bowen's disease and their treatment must wait for subsequent visits or these lesions can be treated in the interim with liquid nitrogen, imiquimod, 5-fluorouricil, or electrodesiccation and curettage.

SCC in this population may be large, deep, aggressive, clinically ill-defined, and have unfavourable histologic features such as poor differentiation, lymphovascular invasion, or perineural invasion. These tumors are known to be more aggressive than in the non-transplant population and prompt evaluation, biopsy, and treatment is the norm.

Management of actinic keratoses with field therapy and destructive modalities is a constant revolving cycle in the transplant patient and similar regimens apply as in the non-transplant population. Curettage, topical retinoids, topical 5-fluorouricil, imiquimod, photodynamic therapy, and others are all employed on rotation.

Concerns about the risk of inducing renal dysfunction with the use of cytokine-inducing topical imiquimod (reported in one case[7]) have not been supported in subsequent trials.[8,9] Five percent imiquimod cream used over 100 cm^2 3 times per week for 16 weeks resulted in no detection of graft rejection in 43 patients.[8]

Regular sunscreen use reduces the development of actinic keratoses and invasive SCC in transplant patients.[10] Sun protection counselling begins on the first visit and builds over time. Lymph nodes are checked at each visit in patients with a history of invasive SCC.

Chemoprophylaxis

The clinician may consider acitretin chemoprophylaxis for any patient whose skin cancer burden is unrelenting. There is a large body of evidence supporting its use.[11,12] Some indications for use include > 5-10 skin cancers per year, few but aggressive SCCs, multiple SCCs in high-risk sites, and the impact of cancer burden/ procedures on mental health and quality of life.

There is ample consensus for the use of low starting doses of 10 mg per day or every second day, which is well tolerated.[12,13] The dose may be titrated up, but waiting for at least three to six months before doing so may be prudent, as up-titration may not be necessary. Incremental increases in dose (i.e. 10 mg/day alternating with 20 mg/ day or even 10 mg/10 mg/20 mg per day in a three day cycle) are much better tolerated than large jumps in dose.

Drug interactions are minimal at low doses. Acitretin can be stopped at any time with the expectation that skin cancers will reappear quickly, but rarely explosively.

Laboratory parameters such as aspartate aminotransferase, alanine transaminase, bilirubin and gamma-glutamyl transferase are followed monthly, and cholesterol and triglycerides are followed every three to six months (more frequently in patients on sirolimus or cyclosporin as these medications also increase triglycerides). Common side effects include brittle nails, sticky skin phenomenon, paronychia (advocate good toenail care from the start), blepharitis, and hair thinning – all of which are mild at low doses but pre-emptive counselling is important. Rare side effects of oral retinoids such as benign intracranial hypertension, psychiatric symptoms, and inflammatory back pain must be discussed. Although it theoretically can affect 'wound healing', acitretin therapy is not interrupted for routine skin surgery. Dose reduction will need to occur if the patient goes back on dialysis. Acitretin is contraindicated in women of childbearing potential; isotretinoin is an acceptable alternative in these patients or in patients who need control of acneiform eruptions (common with prednisone or calcineurin inhibitor

[CNI] use) in addition to skin cancer prophylaxis.[11]

The goal of this treatment approach is to reduce clinically significant keratinocyte carcinoma and actinic keratoses thereby reducing skin cancer burden and all of its potential implications and morbidity for the patient. This is a compelling enough goal for most patients. Direct evidence that acitretin reduces the risk of metastatic disease or mortality is lacking.

Alteration of immunosuppression

Reduction in global immunosuppression is a well-accepted skin cancer prevention strategy.[6] In the SCREEN clinic possible scenarios are discussed as soon as a patient develops their first invasive SCC so that an action plan is in place if clinical progression ensues.

Assessing and interpreting a patient's immunosuppression occurs at each visit and is not time-consuming. Older regimens include azathioprine and cyclosporin. New, better-tolerated, modern regimens contain tacrolimus and mycophenolate mofetil (MMF).

The International Immunosuppression & Transplant Skin Cancer Collaborative (ITSCC) and Skin Care for Organ Transplant Patients Europe Reduction of Immunosuppression Task Force have developed criteria for mild, moderate and severe reductions of immunosuppression.[14] No reductions are recommended for actinic keratoses alone. For renal transplant patients with SCC, mild reductions are indicated when patients develop 1-25 skin cancers per year, or fewer higher-risk SCC tumours. Patients who develop greater than 25 skin cancers per year (considered to have a 5% risk of mortality) or aggressive, high-associated-mortality SCC would be candidates for moderate reductions. Severe reductions are reserved for life-threatening skin cancers (i.e. metastatic disease).

When appropriate, a suggested strategy may include asking the transplant team to consider a reduction in overall global immunosuppression if the patient is medically stable and reduction is not contraindicated. The transplant team is likely waiting to hear from the dermatologist in order to initiate these conversations. Modification of immunosuppression may be quite achievable in circumstances where patients are relatively over-immunosuppressed and could benefit from medication review and reconciliation.

Dermatologists may be asked which drug should be decreased. Azathioprine and calcineurin inhibitors are associated with SCC post-transplant; the most robust evidence is for azathioprine.[3,15] Azathioprine doses can be reduced, or the regimen can be switched to incorporate mycophenolate mofetil instead of azathioprine.[1,14] Cyclosporin and tacrolimus doses or formulations can be titrated to lower target levels in patients whose levels may be running high. The role of MMF in skin cancer is controversial and summarized well by Howard et al.[1] Although considered to be less carcinogenic than azathioprine or the CNIs, MMF has been associated with skin cancer development.[1] Doses may be adjusted from full-dose to half-dose, or half-dose to quarter-dose depending on the circumstances and the patient's baseline dosage. The role of prednisone in photocarcinogenesis remains controversial.[16]

Sirolimus is a mammalian Target of Rapamycin (mTOR) inhibitor that is associated with a reduction in AK and keratinocyte carcinoma in transplant patients.[17] However, potential side effects and complications preclude its consistent use and in the SCREEN clinic sirolimus is considered only when other strategies have failed. Common side effects include fatigue, mouth sores, poor wound healing, leg edema, myelosuppression, hypertriglyceridemia and proteinuria. Nonetheless there are clinical scenarios in which the benefits outweigh the risks and replacing a CNI with sirolimus is an effective strategy.

Adjunctive strategies

Niacinamide (vitamin B3) 500 mg b.i.d. was shown to decrease actinic keratoses and keratinocyte carcinoma in immunocompetent (non-transplant) patients with a history of at least two nonmelanoma skin cancers in the past five years.[18] Niacinamide (also called nicotinamide) is well-tolerated, does not cause flushing, is available over-the-counter, and has an excellent safety profile. A case-control trial in transplant patients demonstrated significant reduction of actinic keratoses[19], but other data in the transplant patient population is lacking. Nonetheless, it is being used, as downsides are few. A Canadian pilot study (SPRINTR trial, ClinicalTrials.gov Identifier: NCT03769285) is a feasibility study currently underway as a precursor to a possible larger pivotal trial of niacinamide chemoprophylaxis in post-transplant skin cancer patients.

Voriconazole and hydrochlorothiazide are two photosensitizing medications highly associated with development of SCC[6,20] and should be avoided.

Although the evidence is very limited, HPV vaccination may be recommended in challenging skin cancer patients. Conceptually this is an exciting possibility considering the known association between SCC and HPV[21], but evidence is limited to case reports. Two immunocompetent patients given the quadrivalent HPV vaccine had a marked decrease in recorded numbers of SCC and basal cell carcinoma (BCC) in the year post-immunization.[22] In addition to systemic vaccine administration, intralesional diluted HPV vaccine was injected twice into three large squamous cell carcinomas in another patient with multiple leg tumours. Eleven months after the first injection all her leg tumours had regressed, and no recurrence was reported at the 24 month follow-up visit.[23]

Pre-transplant considerations

Dermatologists may be asked to provide a readiness-for-transplantation assessment in patients with a history of SCC. This may be prior to their first transplant or retransplantation after graft failure. It may be helpful for clinicians to refer to this excellent consensus statement by Zwald et al to help guide clinical decision making.[24] Patients with a fully treated high-risk SCC (i.e. > 2 cm, poorly differentiated, recurrent, high-risk site) should ideally wait 2 years; if perineural invasion is present, a wait time of 3 years is preferable.

These are just a few of the many ways in which dermatologists can contribute to the nuanced care of post-transplant recipients.

References:

1. Howard MD, Su JC, Chong AH. Skin Cancer Following Solid Organ Transplantation: A Review of Risk Factors and Models of Care. Am J Clin Dermatol. 2018;19(4):585-97.

2. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol. 2006;154(3):498-504.

3. Perez HC, Benavides X, Perez JS, Pabon MA, Tschen J, Maradei-Anaya SJ, et al. Basic aspects of the pathogenesis and prevention of non-melanoma skin cancer in solid organ transplant recipients: a review. Int J Dermatol. 2017;56(4):370-8.

4. Mittal A, Colegio OR. Skin Cancers in Organ Transplant Recipients. Am J Transplant. 2017;17(10):2509-30.

5. Acuna SA, Huang JW, Scott AL, Micic S, Daly C, Brezden-Masley C, et al. Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines. Am J Transplant. 2017;17(1):103-14.

6. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):253-61.

7. Santos-Juanes J, Esteve A, Mas-Vidal A, Coto-Segura P, Salgueiro E, Gomez E, et al. Acute renal failure caused by imiquimod 5% cream in a renal transplant patient: review of the literature on side effects of imiquimod. Dermatology. 2011;222(2):109-12.

8. Ulrich C, Bichel J, Euvrard S, Guidi B, Proby CM, van de Kerkhof PC, et al. Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. Br J Dermatol. 2007;157 Suppl 2:25-31.

9. Ulrich C, Busch JO, Meyer T, Nindl I, Schmook T, Sterry W, et al. Successful treatment of multiple actinic keratoses in organ transplant patients with topical 5% imiquimod: a report of six cases. Br J Dermatol. 2006;155(2):451-4.

10. Ulrich C, Jurgensen JS, Degen A, Hackethal M, Ulrich M, Patel MJ, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol. 2009;161 Suppl 3:78-84.

11. Herold M, Good AJ, Nielson CB, Longo MI. Use of Topical and Systemic Retinoids in Solid Organ Transplant Recipients: Update and Review of the Current Literature. Dermatol Surg. 2019;45(12):1442-9.

12. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):263-79.

13. Ritchie SA, Patel MJ, Miller SJ. Therapeutic options to decrease actinic keratosis and squamous cell carcinoma incidence and progression in solid organ transplant recipients: a practical approach. Dermatol Surg. 2012;38(10):1604-21.

14. Otley CC, Berg D, Ulrich C, Stasko T, Murphy GM, Salasche SJ, et al. Reduction of immunosuppression for transplant-associated skin cancer: expert consensus survey. Br J Dermatol. 2006;154(3):395-400.

15. Jiyad Z, Olsen CM, Burke MT, Isbel NM, Green AC. Azathioprine and Risk of Skin Cancer in Organ Transplant Recipients: Systematic Review and Meta-Analysis. Am J Transplant. 2016;16(12):3490-503.

16. Plasmeijer EI, Sachse MM, Gebhardt C, Geusau A, Bouwes Bavinck JN. Cutaneous squamous cell carcinoma (cSCC) and immunosurveillance - the impact of immunosuppression on frequency of cSCC. J Eur Acad Dermatol Venereol. 2019;33 Suppl 8:33-7.

17. Karia PS, Azzi JR, Heher EC, Hills VM, Schmults CD. Association of Sirolimus Use With Risk for Skin Cancer in a Mixed-Organ Cohort of Solid-Organ Transplant Recipients With a History of Cancer. JAMA Dermatol. 2016;152(5):533-40.

18. Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. N Engl J Med. 2015;373(17):1618-26.

19. Drago F, Ciccarese G, Cogorno L, Calvi C, Marsano LA, Parodi A. Prevention of non-melanoma skin cancers with nicotinamide in transplant recipients: a case-control study. Eur J Dermatol. 2017;27(4):382-5.

20. Rouette J, Yin H, Pottegård A, Nirantharakumar K, Azoulay L. Use of Hydrochlorothiazide and Risk of Melanoma and Nonmelanoma Skin Cancer. Drug Saf. 2020.

21. Gupta R, Rady PL, Doan HQ, Tyring SK. Development of a ß-HPV vaccine: Updates on an emerging frontier of skin cancer prevention. J Clin Virol. 2020;126:104348.

22. Nichols AJ, Allen AH, Shareef S, Badiavas EV, Kirsner RS, Ioannides T. Association of Human Papillomavirus Vaccine With the Development of Keratinocyte Carcinomas. JAMA Dermatol. 2017;153(6):571-4.

23. Nichols AJ, Kirsner RS, Ioannides T. Use of Combination Systemic-Intratumoral HPV Vaccine to Treat Cutaneous Basaloid Squamous Cell Carcinomas-Reply. JAMA Dermatol. 2019;155(1):124-5.

24. Zwald F, Leitenberger J, Zeitouni N, Soon S, Brewer J, Arron S, et al. Recommendations for Solid Organ Transplantation for Transplant Candidates With a Pretransplant Diagnosis of Cutaneous Squamous Cell Carcinoma, Merkel Cell Carcinoma and Melanoma: A Consensus Opinion From the International Transplant Skin Cancer Collaborative (ITSCC). Am J Transplant. 2016;16(2):407-13.