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REVIEW

Skin Cancer in Solid Organ Transplant Recipients: A Review for the Nondermatologist

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Abstract

Solid organ transplant recipients (SOTRs) are at increased risk for the development of skin cancer compared with the general population, which requires consistent monitoring and management from a multidisciplinary team. The aim of this review is to provide a comprehensive overview for nondermatologist clinicians, outlining skin cancer diagnosis, treatment pearls, and skin cancer prevention strategies as they relate to SOTRs.

A comprehensive search of the literature was conducted through the MEDLINE database with search terms including *organ transplantation, transplant recipient, skin cancer, cutaneous neoplasms, management,* and *therapies*. The search was limited to the English language and dates ranging from January 1, 2011, to December 28, 2021. All studies were reviewed for inclusion.

Skin cancer will develop in more than half of SOTRs at some point in their life, most often nonmelanoma skin cancer such as basal cell carcinoma or squamous cell carcinoma. Melanoma and rarer cutaneous malignant neoplasms, such as Merkel cell carcinoma and Kaposi sarcoma, are also more frequent among SOTRs. A multidisciplinary effort at skin cancer screening and patient education is invaluable to prevent skin cancer–related morbidity and mortality in this population of patients. Reduction in immunosuppressive medications and surgical intervention are effective therapeutic approaches, and more novel systemic therapies including G protein–coupled receptor inhibitors and immune checkpoint inhibitors are possible options when traditional treatment approaches are not feasible. Checkpoint inhibitor therapy, however, comes with the risk of allograft rejection.

With a growing and aging SOTR population, it is essential that SOTRs have support from dermatologists and nondermatologists alike in skin cancer prevention and treatment.

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Solid organ transplant recipients (SOTRs) are at increased risk for the development of skin cancer compared with the general population. This increased risk includes many types of cutaneous malignant neoplasms and is highest for cutaneous squamous cell carcinoma (SCC), which some studies estimate to be several hundred times higher than in the general population.[1] The increase in skin cancer in SOTRs is secondary to the long-term immunosuppressive therapy required for transplanted organ survival, which impairs the immune system's ability to monitor cells for atypia. Thus, care for the SOTR requires consistent monitoring by a multidisciplinary team including transplant providers, organ-specific specialists, dermatologists, and the primary care physician. Prevention strategies, treatment options, and our overall understanding of skin cancer development in SOTRs are rapidly expanding. Whereas dermatologists ultimately treat and manage many cutaneous malignant neoplasms in these high-risk patients, an understanding of skin cancer risk, development, and management is

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ARTICLE HIGHLIGHTS

- Organ transplant recipients have a markedly higher risk for skin cancer compared with the general population.
- Skin cancer treatments and chemoprevention may necessitate monitoring of multiple organ systems in a multidisciplinary fashion.
- Strategies to prevent skin cancer development in this population include patient education on photoprotection, regular skin checks, modification of immunosuppression, and treatment of precancerous lesions with appropriate destructive techniques.

important across all members of the patient care team. This shared responsibility is especially heightened in communities with limited dermatology access as primary care may assume responsibility for skin cancer prevention and screening. Herein we provide a comprehensive overview for the nondermatologist medical clinician, outlining skin cancer diagnostic and treatment pearls as they relate to SOTRs as well as skin cancer prevention strategies.

METHODS

A Mayo Clinic Libraries librarian searched the MEDLINE database using the Ovid interface. Search terms included MeSH terms as well as keywords of *organ transplantation, transplant recipient, skin cancer, cutaneous neoplasms, management,* and *therapies*. An English-language search filter was employed. A publication date filter limited the results from January 1, 2011, to the day the search was run, December 28, 2021. Article types in our final analysis include all meta-analyses, systematic reviews, randomized controlled trials, guidelines, and prospective and retrospective studies. All articles were evaluated, and articles with robust evidence or those with novel concepts were cited in this review.

SKIN CANCER TYPES AND TREATMENTS

In both SOTRs and the immunocompetent patient, baseline skin pigmentation, genetic predisposition, age, male sex, and previous exposure to ultraviolet (UV) light play a role in skin cancer development.[2] Risk factors unique to organ transplant recipients include age older than 50 years at the time of transplant, pretransplant skin cancer or actinic keratosis history, human papillomavirus (HPV) infection, and thoracic organ transplant.[3-6] Skin cancer will develop in more than half of SOTRs at some point in their life, most often nonmelanoma skin cancer (NMSC) such as basal cell carcinoma (BCC) or SCC, as transplant patients are estimated to have a 10-fold and 65- to 100-fold increased risk of these malignant neoplasms, respectively.[7] Melanoma prevalence is also increased in the organ transplant population,[8] as are rare cutaneous malignant neoplasms, such as Merkel cell carcinoma and Kaposi sarcoma. In this population, early recognition of skin cancer and prompt referral to a dermatologist for definitive treatment are paramount to avoid locally advanced and metastatic disease.

Actinic Keratosis (Precancer)

Overview. Actinic keratosis (AK) is a premalignant area of dysplastic keratinocytes manifested as erythematous, scaling macules and patches (Figure A). It is considered a "precancerous" lesion because of its ability to transform into invasive SCC. However, the exact rate at which it becomes malignant or spontaneously regresses is uncertain as estimates for malignant transformation range from less than 1% to 10%.[9,10] Patients with a history of NMSC have higher rates of AK progression into skin cancer.[9] Transplant recipients with systemic immunosuppression often have a higher burden of AKs than the general population does, with a greater likelihood for development of SCC. The risk is estimated to be at least 100-fold that of immunocompetent patients.[11]

Treatment. Procedural therapy for discrete AKs includes techniques such as cryotherapy, curettage, and electrodessication. Field therapy, which is treatment of an entire surface area of a given anatomic location, such as the face, is an important and widely

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used approach in addressing diffuse AKs, field cancerization, and prevention. Commonly used techniques for field therapy include photodynamic therapy and topical therapies, such as 5-fluorouracil (5-FU), 5-FU with calcipotriene, and imiquimod.

Squamous Cell Carcinoma

Overview. The most common malignant neoplasm seen in SOTRs is cutaneous SCC. Squamous cell carcinoma arises from keratinocytes and typically is manifested as a crusted or scaly, erythematous papule (Figure B).[12] Organ transplant patients are at risk for worse outcomes, resulting in increased morbidity and a skin cancer–specific mortality that is 9 times higher than in the general population.[7,13,14] There appears to be an especially increased risk of SCC development among thoracic organ recipients, probably because of the need for higher doses of immunosuppressive medication.[14,15] They also have a higher risk of eruptive squamous atypia or keratoacanthomas, which are rapidly growing, crater-shaped tumors that arise from squamous epithelial cells.[16]

The American Joint Committee on Cancer, 8th edition (AJCC8) and the Brigham and Women's Hospital (BWH) staging systems are most widely used for cutaneous SCC. The BWH staging is based on several risk factors, including tumor size, invasion beyond subcutaneous fat, large-caliber perineural invasion, and poor histologic differentiation. In the AJCC8 classification system, risk factors are tumor size and presence of bone invasion or perineural or deep invasion. Neither staging system incorporates immunosuppression as a high-risk feature. The National Comprehensive Cancer Network (NCCN) categorizes SCCs into low risk, high risk, and very high risk on the basis of recurrence status, size, histologic features, and patient features (including immunosuppression). Per the NCCN, all immunosuppressed patients fall within at least the high-risk category as risk categorization is based on the highest risk factor present (Table 1).

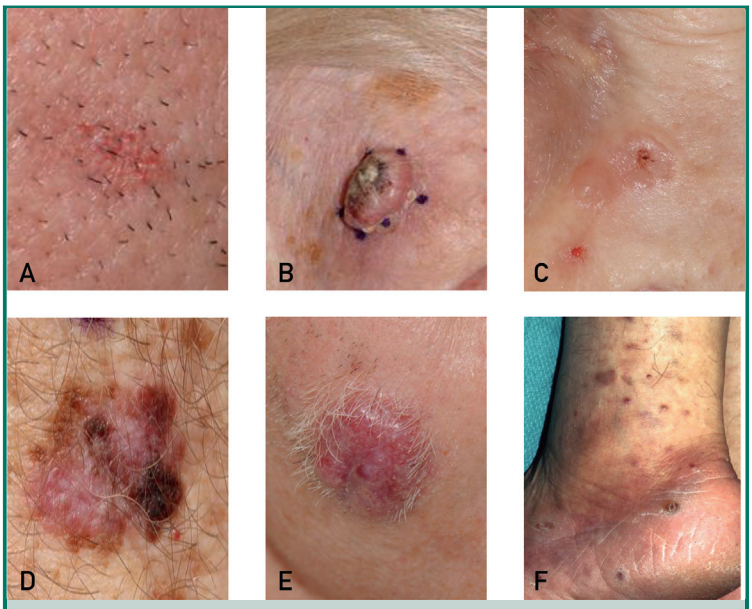

FIGURE. Cutaneous malignant neoplasms and precancers. A, Actinic keratosis. B, Squamous cell carcinoma. C, Basal cell carcinoma. D, Malignant melanoma. E, Merkel cell carcinoma. F, Kaposi sarcoma.

Studies have found that high-risk tumors are associated with increased risk of nodal metastases.[17] Poor outcomes, defined by local recurrence, nodal metastases, and disease-specific death, are frequent among SOTRs with advanced tumor stage as defined by either AJCC8 or BWH staging.[18]

Treatment. Reduction of immunosuppressive medications has been reported to be an effective therapeutic strategy for transplant-associated skin cancer.[19] However, decreasing immunosuppression can also increase the risk of transplanted organ rejection, so the risks and potential benefits of this approach must be considered in partnership with transplant specialists and close monitoring.

For high-risk tumors, both Mohs surgery and wide local excision can be considered. For tumors of very high risk, it is recommended that patients undergo Mohs micrographic surgery or complete circumferential peripheral and deep margin assessment for the highest likelihood of local tumor control. With Mohs surgery or

complete circumferential peripheral and deep margin assessment, 100% of the margin is assessed by en face processing compared with approximately 1% of the margin assessed with standard (bread-loafed) processing with a wide local excision. The advantages of Mohs surgery are the complete histologic evaluation of margins, the ability to confirm clear margins at the time of surgery before tissue rearrangement for reconstruction, and the ability for tissue sparing in critical anatomic locations.

In patients with locally advanced or metastatic cutaneous SCC, a multidisciplinary discussion involving dermatology, head and neck surgery, and surgical oncology specialists helps determine the most appropriate resection strategy. The radiation oncologist will guide the plan and administration of adjuvant or palliative radiation. Input from a medical oncologist is essential for managing systemic treatments. Epidermal growth factor receptor inhibitors, such as cetuximab and panitumumab, are a systemic option for widely metastatic disease. Common adverse effects include papulopustular eruptions and paronychia. Immune checkpoint inhibitors (ICIs), such as cemiplimab, target programmed cell death 1 (PD-1) and have been approved for nonsurgical candidates with locally advanced SCC or metastatic SCC. Currently, data regarding the efficacy and safety of ICIs among SOTRs are limited to case series and reports. For example, use of ICIs in transplant recipients with locally advanced or metastatic SCC has demonstrated improved overall and disease-specific survival in several small retrospective reviews.[20,21] The use of ICIs in SOTRs carries a substantial risk of transplanted organ rejection, which can be life-threatening in this population,[20] and thus further research on optimization of these medications is necessary.

For eruptive keratoacanthomas, Food and Drug Administration—approved treatments in SOTRs are lacking. Off-label treatments include intralesional 5-FU, intralesional methotrexate, intralesional bleomycin, and systemic retinoids such as acitretin. The safety of intralesional therapies has not been studied in transplant patients in large retrospective cohort studies.[16] Surgical interventions, such as wide local excision, Mohs micrographic surgery, or electrodessication and curettage, are frequently employed.

Basal Cell Carcinoma

Overview. Basal cell carcinoma is the most common type of skin cancer among immunocompetent patients, although its incidence is lower than that of SCC in immunosuppressed patients.[1] There are several different subtypes of BCC; most occur on sun-exposed areas. Subtypes commonly seen include superficial, nodular, micronodular, infiltrative, morpheaform, and pigmented. Early BCCs are classically manifested as pearly, pink papules with a rolled border and telangiectasia, whereas advanced tumors can be large plaques or nodules with central ulceration and a raised, indurated border (Figure C).[12]

Treatment. Treatment of BCC in SOTRs is approached as in immunocompetent patients. Unlike SCCs, BCCs have a much more limited biologic potential for metastasis and death, with treatment emphasis instead focused on limiting morbidity from disease. The most common treatment approaches are superficial destructive modalities and surgical techniques including curettage, cryosurgery, wide local excision, and Mohs micrographic surgery. Systemic agents are also available for locally advanced and metastatic BCC.[22]

Systemic therapies include vismodegib and sonidegib, which are smoothened inhibitors. Smoothened is a G protein—coupled receptor in the hedgehog pathway whose overactivity is implicated in the formation of BCC. These agents have not been well studied in SOTRs, with evidence currently limited to case reports.[23] Vismodegib has been used successfully to treat advanced BCC in a heart transplant patient concurrently receiving cyclosporine in addition to multiple renal transplant patients.[23-25] As for SCC, the ICI cemiplimab has been

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approved as the first immunotherapeutic regimen for locally advanced BCC. According to a phase 2 trial conducted by Stratigos et al, [26] cemiplimab was reported to have a clinically significant benefit among patients who were previously treated with hedgehog inhibitors but are no longer candidates for this medication. Investigations examining its safety and efficacy among SOTRs are limited, and therefore its use in this population is cautioned.[27]

Melanoma

Overview. Melanomas are malignant neoplasms of melanocytes, with significant potential for morbidity and mortality among immunocompetent and immunosuppressed patients. They can have a variety of presentations, including pigment variations within the same lesion and irregularities of shape or size. Melanoma may appear as a dark papule in the nodular form, a multipigmented patch or plaque in the superficial spreading form, an irregularly pigmented patch in the lentigo maligna form, or spreading lesions in the palms or soles in the acral lentiginous form (Figure D).[12] Organ transplant recipients have an increased risk of melanoma in comparison to the general population, estimated to be approximately 2.5 to 5 times higher for SOTRs in general, with a particularly increased risk in Black patients.[7] Organ transplant recipients with melanoma in situ or thin melanomas (<1 mm Breslow thickness) have survival and recurrence rates similar to those of immunocompetent patients.[8] However, transplant patients are more likely to present with advanced melanoma and to have an increased rate of death compared with matched controls.[28] These findings suggest that melanoma has a more aggressive disease course among transplant recipients.[28]

Staging of melanoma is primarily dependent on Breslow depth and secondarily on presence of ulceration. Breslow depth is a histologic measurement from the granular layer to the deepest invasive portion. Gene expression profiling is a newer tool designed to help with prognostication of melanoma. It has potential to expand our current staging system, but it is not yet the mainstay of treatment and requires further study and validation.[29]

Treatment. Melanomas are most often treated with wide local excision with margins determined by the Breslow depth. In anatomically constrained areas, Mohs micrographic surgery may be used in combination with immunostains. Multiple studies reported improved rates of disease-free survival and overall survival in the Mohs surgery cohort compared with wide local excision.[30]

Management of melanoma in SOTRs is similar to that in immunocompetent patients of similar stage, with Breslow depth determining margins for surgical excision and need for sentinel lymph node biopsy.[31] For stage T1b tumors and above (Breslow depth of 0.8 to 1.0 mm with or without ulceration or <0.8 mm with ulceration), sentinel lymph node biopsy is recommended. Lymph node biopsy results have an impact on staging, prognostication, and treatment. Metastatic melanomas that have *BRAF* mutations can be treated with BRAF inhibitors such as dabrafenib.[32] Immunotherapy for melanoma has a substantial risk of transplant rejection in SOTRs; however, the use of checkpoint inhibitors is becoming more prevalent in SOTRs as a final option in patients who have failed to respond to all other possible therapies. Ipilimumab, a cytotoxic lymphocyte antigen 4 inhibitor approved for the treatment of melanoma in immunocompetent patients, has several reports of safe administration in liver and kidney transplant recipients, whereas PD-1 inhibitors have been associated with a relatively higher risk of acute rejection.[33,34] Although minimizing transplant immunosuppression is a well-studied therapeutic approach for NMSC, its efficacy for melanoma has not been as comprehensively investigated.[8,19]

Merkel Cell Carcinoma

Overview. Merkel cell carcinoma (MCC) is an aggressive primary cutaneous neuroendocrine carcinoma with a predilection for the head and neck region of White patients older

than 50 years and has a significant risk of metastasis. It typically is manifested as a rapidly growing red to purple, dome-shaped, smooth nodule and is often asymptomatic (Figure E). There is a positive association of MCC with UV radiation exposure and immunosuppression. Immunocompromised patients with T-cell dysfunction have a markedly increased incidence of this disease as MCC is 5 to 10 times more likely to develop in SOTRs.[35] Merkel cell polyomavirus is a human polyomavirus that was discovered in 2008, and its oncogenic role in the pathogenesis of 80% of MCCs has been reported in several studies.[36]

Treatment. Current treatment guidelines from the NCCN recommend management of the primary tumor with wide local excision with 1- to 2-cm margins, with or without adjuvant radiation therapy. Notably, a sentinel lymph node biopsy is recommended for clinically node-negative tumors. Immunotherapy is an alternative approach based on the identification of several novel therapeutic targets identified in the Merkel cell polyomavirus–specific cellular immune response.[37] Avelumab and pembrolizumab are Food and Drug Administration approved for treatment of recurrent locally advanced or metastatic MCC; however, the significant risk of transplanted organ rejection and loss associated with checkpoint inhibitors in SOTRs must be considered.[38,39]

Kaposi Sarcoma

Overview. Kaposi sarcoma (KS) is a malignant vascular tumor associated with reactivation of latent human herpesvirus 8 (HHV-8) due to immunosuppression and, less commonly, through donor-derived infection. It is clinically manifested as erythematous to violaceous macules, patches, plaques, papules, or nodules on the skin, mucous membranes, lymph nodes, or other organs (Figure F). Because of its relationship to immunosuppression, there is a 200-fold increased risk of KS development in transplant recipients.[40] Rates of KS development after transplant vary by geographic region. For example, among renal transplant recipients, KS development is less common in northern and western parts of the world (approximately 0.5% of SOTRs) and higher in Mediterranean countries and some parts of the Middle East (approximately 5% of SOTRs).[41] This is reflective of HHV-8 being endemic to certain regions of the world.

Treatment. A multicenter retrospective study examining treatment of SOTRs diagnosed with KS found that more than 80% of the patients examined had a good treatment response. This suggests that KS after organ transplant is a manageable disease. Of these patients, 95% were treated by reducing organ transplant immunosuppression medications, either as the sole treatment or in conjunction with conversion to mechanistic target of rapamycin (mTOR) inhibitors or use of chemotherapy agents.[40] As such, reducing immunosuppression is the cornerstone of posttransplant KS therapeutic management. Systemic chemotherapy includes pegylated liposomal doxorubicin or other cytotoxic agents, such as vinblastine, bleomycin, taxane, etoposide, and gemcitabine. The role of antiviral therapy against HHV-8 is limited.[40,42]

INTERVENTIONS FOR SKIN CANCER PREVENTION

Prevention is the cornerstone of skin health in transplant recipients. Prevention strategies require active involvement of the patient and the patient's medical team. This includes education, practicing photoprotective measures, pharmaceutical and procedural interventions to prevent skin cancer, and regular skin cancer screenings. A dermatology referral is often made at the time of organ transplant; however, the critical role of early skin cancer prevention and education is often deferred to primary care. Detailed education should begin before potential organ transplant as UV light exposure is accumulated during a lifetime.

Pretransplant Screening

Transplant teams should perform a risk assessment for all SOTRs to determine the

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TABLE 1. Cutaneous Squamous Cell Carcinoma "High-Risk" Features

	AJCC high-risk features	NCCN high-risk features	BWH high-risk features
Anatomic location of primary tumor	Tumor located on ear or hair-bearing lip	Tumor larger than 10 mm on the forehead, scalp, cheek, and neck *or* tumor larger than 6 mm on the ears, eyelids, nose, temple, lips, and periauricular or periorbital area	
		Site of chronic inflammation or prior radiation treatment	
Histologic/clinical features	Poorly differentiated or undifferentiated	Moderately or poorly differentiated	Poorly differentiated
		Poorly defined borders	
Depth/tumor growth	Perineural invasion	Rapidly growing tumor	Perineural invasion ≥0.1 mm
	Tumor depth >2 mm		Tumor invasion beyond fat
	Clark level >IV		Tumor diameter ≥2 cm
Other features		Recurrent tumor	
		Immunosuppression treatment	
		Neurologic symptoms	

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; NCCN, National Comprehensive Cancer Network.

likelihood for development of skin cancers during the initial evaluation. Any preexisting skin cancer or precancers should be promptly treated before transplant. Skin cancers during the pretransplant period have bearing on posttransplant risk and screening recommendations.

Posttransplant Screening

The frequency of posttransplant skin evaluations varies by patient risk factors. A 2019 expert panel established guidelines for initial skin cancer screening in SOTRs without a previous history of skin cancer.[43] High-risk patients included heart or lung transplant recipients, patients older than 50 years at time of transplant, and male patients. High-risk White patients should begin regular screenings within 2 years after transplant, and all Hispanic, Asian, and high-risk Black or African descent patients should begin screening within 5 years after transplant. There was no consensus in low-risk Black SOTRs. Patients with a prior history of skin cancer should continue skin cancer screenings as directed by their dermatologist.[43]

Most posttransplant clinical practice guidelines recommend at least annual skin cancer screening for the remainder of life; more frequent screening by a dermatologist may be necessary in high-risk patients. Some guidelines suggest that screening can be performed by primary care providers for low-risk patients.[44]

The primary care physician plays an important role in performing initial skin checks and ensuring that patients are evaluated by a dermatologist within the appropriate time frame. A population study of 10,183 SOTRs in Canada reported poor adherence to regular dermatology visits, with only 2.1% adhering to annual dermatology visits during the 18-year evaluation period.[45] Primary care providers are uniquely positioned to encourage appropriate skin cancer evaluations to prevent skin cancer—related morbidity and mortality in this population.

Posttransplant skin cancer screenings should include a full-body skin examination, including evaluation of oral mucosa and genitalia. Non-White SOTRs have been reported to have a higher incidence of cutaneous malignant disease involving the genitalia, including genital SCC associated with high-risk HPV subtypes.[46]

Patient Education

Counseling and education of SOTRs about modifiable risk factors and skin cancer

detection strategies are critical (Table 2). All clinicians involved in care of SOTRs can have an impact on encouraging skin cancer prevention. SOTRs who are advised to use sunscreen by any health care professional are significantly more likely to practice these photoprotective measures than those who are not.[47] However, a 2020 systematic review found that educational intervention for limiting sun exposure in transplant recipients improved sun safety measures but did not lead to ultimate reduction in skin cancer.[48] Further investigation on this topic is warranted to identify the most effective means of educational intervention.[48,49]

TABLE 2. Skin Cancer Education and Counseling Highlights for SOTR

- Sun protection with high SPF sunscreen (even if it is cloudy)
- Use of physical UV light barriers, such as photoprotective clothing, hats, sunglasses
- Avoidance of exposure to UV light by limiting outdoor activity during peak daylight (10 AM to 4 PM)
- Abstinence from tanning or artificial UV sources
- Education on the ABCDE rule for skin cancer identification: asymmetry, border, color, diameter, elevation/evolving
- Monthly self-examination of skin and annual skin examination by a dermatologist or primary care physician experienced with skin cancer

SOTR, solid organ transplant recipient; SPF, sun protection factor; UV, ultraviolet.

POSTTRANSPLANT PHARMACEUTICAL MODIFICATIONS

After organ transplant, patients must begin immunosuppressive medication to prevent transplanted organ rejection. Patients often begin with induction therapy at the time of transplant and then transition to lifelong immunosuppressive maintenance therapy. Additional antimicrobial prophylaxis is frequently necessary, given the increased risk for infection with immunosuppression.

Maintenance immunosuppression therapy often includes the combination of calcineurin inhibitors and mycophenolate mofetil (MMF). Older immunosuppressive agents, such as azathioprine and cyclosporine, have been associated with higher risk of posttransplant cancer, including cutaneous SCC.[1,16,50] Current evidence investigating the effect of various induction immunosuppression therapies on the risk of skin cancer is inconclusive.[16]

Modification of Immunosuppression

It is well established that increased duration and potency of immunosuppressive regimens are associated with an increased incidence of skin cancer in SOTRs.[51] Several studies have suggested that conversion from calcineurin inhibitors to mTOR inhibitors, including sirolimus and everolimus, reduces incidence of posttransplant NMSC.[7,52-61] One systematic review evaluating preventive measures for skin cancer development in SOTRs found that conversion to an mTOR inhibitor from other immunosuppressants was the only intervention to effectively prevent skin cancer.[2] However, there is evidence of higher overall mortality and medication adverse events with the use of mTOR inhibitor therapy.[48,62-65] Therefore, the risk-benefit balance has to be considered with mTOR therapy.

There are also data that transitioning to MMF monotherapy decreases risk of posttransplant NMSC,[66] and some studies have supported a similar finding with mycophenolic acid, the active form of MMF.[67] Based on these studies, early optimization of immunosuppressive regimens with transition to mTOR inhibitors or MMF may help decrease the risk of posttransplant skin cancers.

Modification of Antimicrobial Prophylaxis

The antifungal medication voriconazole, which is often used for fungal prophylaxis, particularly after lung transplant, has been associated with as much as a 73% increased risk for development of cutaneous SCC. This is believed to be secondary to photosensitizing properties of this medication. Posaconazole appears to have a better safety

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profile, especially in patients at high risk of skin cancer development.[7,68]

PHARMACEUTICAL SKIN CANCER PREVENTION

Whereas regular screening and photoprotective measures are critical in SOTRs, additional medical interventions can be used to actively reduce the risk of skin cancer development. Actinic keratoses are precursors to SCCs. Therefore, proactive treatment of these precancerous lesions can greatly reduce risk of SCC development. For patients with many AKs or evidence of extensive damage from sun-exposed skin, individual destruction of lesions can be extremely burdensome, and patients often need to return for repeated treatments. In these patients, field treatment can be extremely useful and efficient in preventing skin cancer development.

Topical Therapy

Topical 5-FU, imiquimod, and diclofenac have been found to be safe and effective field treatments of SOTRs. Fluorouracil 5% cream inhibits thymidylate synthetase, an enzyme implicated in DNA synthesis, and topical application results in lesional inflammation and superficial erosion. Topical imiquimod 5% cream modifies immune response with direct action by binding to Toll-like receptors 7 and 8 on macrophages, monocytes, and dendritic cells and indirectly by release of local cytokines. Application produces local inflammation, and patients may report influenza-like symptoms. Topical diclofenac sodium 3% gel in hyaluronic acid is a nonsteroidal anti-inflammatory drug that inhibits inducible cyclooxygenase 2 and reduces prostaglandin synthesis. The mechanism of action of topical diclofenac in the treatment of AKs is not fully understood. A 2019 systematic review of field-directed regimens in SOTRs (including 5-FU, imiquimod, and diclofenac) found complete clearance rates of 27.5% to 62.1% for imiquimod, 41% for diclofenac, and 11% for 5-FU.[69] Topical treatments can be made more effective by wrapping the area with dressings under occlusion after medication application. These "chemowraps" provide more effective clearance of AKs and can be used to better delineate surgical margins of invasive carcinoma.[70]

The combination of 5-FU and calcipotriene offers the advantage of a shorter treatment course compared with 5-FU alone. Tirbanibulin 1% ointment is a newer agent approved for topical treatment of AKs with a relatively short 5-day treatment course. Tirbanibulin works as an inhibitor of microtubules and SRC kinase signaling.[71] There are currently no studies examining use of these agents specifically in SOTRs.

Photodynamic Therapy

Photodynamic therapy (PDT) combines light energy with topical photosensitizers that generate cytotoxic reactive oxygen species and have a tumoricidal effect on abnormal cells. Photodynamic therapy has had clearance of AKs at a rate of 40% to 76.4%.[69]

Topical photosensitizers commonly used in PDT include 5-aminolevulinic acid and methyl aminolevulinate.[72] A 2019 meta-analysis examined the role of PDT in the prevention and treatment of AKs and SCC in SOTRs and found favorable response rates.[73] There appears to be a similar response to PDT in SOTRs and immunocompetent patients; however, SOTRs have higher rates of recurrence after treatment.[74] Daylight PDT offers a convenient and effective skin cancer prevention strategy, allowing patients to use natural sunlight to activate topical photosensitizers. A 2020 randomized, intrasubject controlled trial using a split-face design to directly compare daylight PDT with cryotherapeutic destruction of lesions found a reduction in new lesions with daylight PDT and reported a patient preference for the PDT treatment over cryotherapy.[75] Another trial found improved clearance rates in pretreating areas with ablative fractional laser before performing daylight PDT with a median complete response of 74% across all AK grades in combined treatment vs 46% in daylight PDT alone after 3 months.[76] Overall, PDT offers an effective option for skin cancer prevention; however, before

initiation of this treatment, patients should be advised of the expected reaction to treatment, which can be uncomfortable: inflammation, skin redness and peeling, discomfort (burning and stinging), and crusting or blistering of lesions.[75]

Systemic Chemoprevention

Systemic chemoprevention with agents such as oral acitretin, nicotinamide, and capecitabine (a 5-FU prodrug) is another method to decrease the risk of posttransplant NMSC. A 2020 meta-analysis limited to placebo-controlled, randomized controlled trials evaluated the efficacy of acitretin and nicotinamide in the prevention of BCC, SCC, and AK in SOTRs and found a significant risk reduction. No significant difference was found between acitretin and nicotinamide.[77]

Oral acitretin is generally started at a low dose of 10 mg daily and up-titrated as tolerated, not exceeding 30 mg daily.[78] Its cancer-protective effects appear to be limited to when the patient is receiving the medication. It has several adverse effects, including teratogenicity, mucocutaneous xerosis, hair loss, liver toxic effects, lipid abnormalities, and myalgia or arthralgia, that may limit its use.

Nicotinamide is generally well tolerated. A dose of 500 mg twice daily has been found to have protective effects against UV radiation and enhancement of DNA repair, reducing the incidence of AK and NMSC. A study assessing the efficacy of nicotinamide 500 mg daily in a small cohort of SOTRs reported significant reduction in AK size in 88% of patients and complete clinical regression in 42%. Within the control group, 91% had an increase in AK size or new AKs, and 7 preexisting AKs (among 19 patients) progressed to SCC.[79] Adverse effects of nicotinamide include allergic reaction, gastrointestinal intolerance, muscle pain, and liver toxic effects at high doses. As with oral retinoid therapy, the chemopreventive effects of nicotinamide are not maintained after cessation. Both nicotinamide and acitretin require continuous administration for chemoprevention and avoidance of rebound NMSC.

Oral capecitabine is a prodrug that is converted to its active form 5-FU in the liver. A systematic review of capecitabine use in SOTRs found low-dose oral capecitabine to be associated with at least a 50% reduction in SCCs during the first 12 months of treatment in addition to a reduction in AKs.[80] Adverse effects included fatigue, nausea, vomiting, diarrhea, hand-and-foot syndrome, anemia, weight loss, cardiomyopathy, gout, and decreased renal function, which may limit the use of this medication.[80-82]

Future and Novel Approaches

Future investigations include evaluating the role of HPV vaccination in the prevention and treatment of SCC. Human papillomavirus has been associated with NMSC development, with HPV DNA found in 80% of NMSCs in immunosuppressed patients, including 50.9% to 93.3% of SCCs.[83] Currently available HPV vaccines are efficacious in preventing high-risk HPV infection associated with cervical, anogenital, and oropharyngeal cancer in addition to providing partial cross-protection against other HPV types. Novel vaccines that offer cross-activity against other HPV types are under development and may help prevent development of SCC in SOTRs.[84]

T4 endonuclease V (T4N5) is an enzyme involved in DNA repair after exposure to UV radiation with a current study investigating the efficacy and safety of T4N5 lotion in the prevention of NMSC in SOTRs. Clinical trials investigating afamelanotide, a synthetic α-melanocyte—stimulating hormone, and the development of keratinocyte carcinomas in SOTRs are also ongoing.[16]

Immune checkpoint inhibitors are a potential treatment option for metastatic or locally advanced skin cancer in SOTRs; however, they carry a substantial risk of transplanted organ rejection. Furthermore, there is not a validated protocol for balancing the immunosuppression required in organ transplant with the heightened immune activity caused by ICIs. A systematic review of organ transplant recipients who received treatment with ICIs, including PD-1, programmed death ligand 1, and cytotoxic lymphocyte antigen 4 inhibitors, reported an overall transplanted organ rejection rate of 41% and transplanted

organ failure in 71% of those patients who experienced rejection. Risk was lowest with ipilimumab (23%) and highest with PD-1 inhibitors, including nivolumab (54%) and pembrolizumab (39%).[34] A case series by Danesh et al [85] suggested that perinfusional corticosteroid administration (pulsed corticosteroids around the time of ICI infusion or low-dose corticosteroid treatment after infusion) may be a promising therapy to prevent transplant rejection. The substantial risk of transplanted organ rejection and loss should be discussed with patients before initiation of treatment with ICIs. At this time, these medications are typically reserved for patients who have failed to respond to all other treatment options.

Several smaller trials reported some additional possibilities for future direction of care. A pilot trial looking at a small cohort of lung transplant recipients randomly assigned to supplementation with omega-3 fatty acid or placebo found some promise in using omega-3 fatty acid supplementation in skin cancer prevention.[86] Novel topical therapies containing DNA repair enzymes may be effective in AK treatment in SOTRs; however, better results were observed in immunocompetent patients than in SOTRs (54.7% reduction in mean number of AKs in immunocompetent patients compared with 36.7% among SOTRs).[87]

CONCLUSION

A cornerstone of long-term survival after organ transplantation is skin cancer prevention and treatment, which warrants attention from all clinicians involved in the care of SOTRs. The nondermatologist should be familiar with prevention and treatment modalities for skin cancer and precancerous lesions and their unique risks and varied efficacy in SOTRs compared with immunocompetent patients. Patients should be encouraged to exercise skin cancer prevention strategies and to follow up regularly with a dermatologist. As our SOTR population grows and ages, future prospective research targeting SOTR-specific skin cancer treatment is needed to guide our care of this unique population. Although not yet standard of care, future novel medications, supplements, and vaccination may become a mainstay of prevention and treatment.

POTENTIAL COMPETING INTERESTS

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland provides consultative advice to AiZtech; AstraZeneca UK Limited; Eli Lilly and Company; Emergent Biosolutions; Exelixis, Inc.; Genevant Sciences, Inc.; GlaxoSmithKline; Janssen Global Services, LLC; Medicago USA; Merck & Co. Inc.; Moderna; Novavax; Pfizer-BNT; Regeneron Pharmaceuticals, Inc.; Sanofi; Syneos Health; and Vyriad. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies. Dr. Poland holds patents related to vaccinia, influenza, and measles peptide vaccines. Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies. Dr. Poland is an adviser to the White House and World Health Organization on Covid-19 vaccines and monkeypox.

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Abbreviations and Acronyms: **AK,** actinic keratosis; **BCC,** basal cell carcinoma; **5-FU,** 5-fluorouracil; **HHV-8,** human herpesvirus 8; **HPV,** human papillomavirus; **ICI,** immune checkpoint inhibitor; **KS,** Kaposi sarcoma; **MCC,** Merkel cell carcinoma; **MMF,** mycophenolate mofetil; **mTOR,** mechanistic target of rapamycin; **NCCN,** National Comprehensive Cancer Network; **NMSC,** nonmelanoma skin cancer; **PD-1,** programmed cell death 1; **PDT,** photodynamic therapy; **SCC,** squamous cell carcinoma; **SOTR,** solid organ transplant recipient; **UV,** ultraviolet

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