Risk of melanoma and nonmelanoma skin cancer with immunosuppressants, part I: Calcineurin inhibitors, thiopurines, IMDH inhibitors, mTOR inhibitors, and corticosteroids

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Learning objectives

After completing this learning objective, the reader will be able to better discuss this aspect of the literature.

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Jeremy Brauer, MD, FAAD is a consultant for Cutera, Inc. and Solta Medical and receives honoraria. Matthew Zirwas, MD, FAAD is a consultant and investigator for Galderma Global and receives honoraria and grants/research funding. He is also a consultant, speaker, and investigator for Leo Pharma and receives honoraria and grants/research funding and is a consultant for L'Oreal USA Inc. and receives honoraria.

All relevant financial relationships have been mitigated.

Immunosuppression is a well-documented risk factor for skin cancer, as exemplified by the 65- to 250-fold higher squamous cell carcinoma risk, 10-fold higher basal cell carcinoma risk, and 0 to 8-fold higher melanoma risk in solid organ transplant recipients (SOTRs) receiving potent, prolonged courses of immunosuppressive therapies. Numerous immune system components have been shown to either suppress or promote tumor growth, and immunosuppressive drugs may have additional effects on proliferative pathways independent of the immune system. Thus, evaluation of the specific regimen by the dermatologist is key for assessing skin cancer risk in each patient. In the present manuscript, the immune-mediated mechanisms of skin cancer development and regression are first reviewed. Next, a synthesis of the evidence shows the differing effects of immunosuppressive agents commonly used in SOTRs on melanoma and nonmelanoma skin cancer risk. These include systemic calcineurin inhibitors, thiopurines, IMDH (inosine monophosphate dehydrogenase) inhibitors, mTOR (mammalian target of rapamycin) inhibitors, and systemic corticosteroids. Finally, recommendations for skin cancer screening in SOTRs are discussed. We further offer recommendations for select nontransplant patients who may benefit from routine skin cancer screening due to risks associated with specific immunosuppressant exposure, and we propose evidence-based strategies for minimizing high-risk immunosuppressant use in clinical practice. (J Am Acad Dermatol 2023;88:521-30.)

Key words: general dermatology; immunosuppressant; medical dermatology; melanoma; nonmelanoma skin cancer; skin cancer screening; transplant.

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Funding sources: None.

IRB approval status: Not applicable.

Patient consent: Not applicable.

Accepted for publication November 15, 2022.

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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2022.11.044

Date of release: November 2022.

Expiration date: November 2025.

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Abbreviations used:

BCC:	basal cell carcinoma
BP:	bullous pemphigoid
CLE:	cutaneous lupus erythematosus
CNI:	calcineurin inhibitor
CTLA-4:	cytotoxic T lymphocyte antigen 4
DM:	dermatomyositis
FSGS:	focal segmental glomerulosclerosis
GVHD:	graft-versus-host disease
HSCT:	hematopoietic stem-cell transplant
IBD:	inflammatory bowel disease
IMDH:	inosine-5′-monophosphate dehydrogenase
LAM:	lymphangioleiomyomatosis
MDSC:	myeloid-derived suppressor cell
MG:	myasthenia gravis
MMF:	mycophenolate mofetil
mTOR:	mammalian target of rapamycin
NK:	natural killer
NMSC:	nonmelanoma skin cancer
OR:	odds ratio
PM:	polymyositis
PUVA:	psoralen and ultraviolet A
RA:	rheumatoid arthritis
RCC:	renal cell carcinoma
RR:	relative risk
SCC:	squamous cell carcinoma
SOTR:	solid organ transplant recipient
Th1:	type 1 CD4+ T cell
Th2:	type 2 CD4+ T cell
T reg:	T regulatory cell
TSC:	tuberous sclerosis complex
UC:	ulcerative colitis
UVR:	ultraviolet radiation

MECHANISMS OF SKIN CANCER DEVELOPMENT IN IMMUNOSUPPRESSION

Key points

- Suppression of various immune system components can sway the immune response in favor of, or in opposition to, carcinogenesis, tumor progression, and metastasis.
- Immunosuppressive drugs may have additional actions on antiproliferative or cancer-promoting pathways independent of the immune system.
- Evaluation of individual immunosuppressive agents is key for appropriately assessing a patient's risk.

Antitumor and protumor effects of immune system components. The immune system has the capacity to both oppose and accelerate tumor growth and progression. The overall effect depends on the balance of relevant immune system components (Fig 1). Briefly, type 1 CD4+ (Clusters of differentiation 4) T cells (T helper type 1 [Th1]) activate CD8+ cytotoxic T cells to destroy tumors, while type 2 CD4+ T cells (Th2) contribute to B-cell-mediated antibody production, shifting the system away from cell-mediated tumor defenses.[1] CD4+ T regulatory cells (T regs) facilitate tumor growth by blocking cytotoxic CD8+ T-cell activation. The mechanism is suspected to involve T reg expression of CTLA-4 (cytotoxic T lymphocyte antigen 4), a T-cell inhibitory signal. T regs also weaken innate antitumor immunity by inhibiting natural killer (NK) cell responses. Inflammation upregulates T reg activity via prostaglandin E2.[1]

The Th17 pathway likely also contributes to tumor growth. Interleukin (IL)-23 activates Th17 cells, which produce IL-17 and a cascade of pro-inflammatory cytokines shown to suppress cytotoxic immunity. Additionally, IL-23 decreases tumor infiltration by CD8+ T cells.[2] B cells have both protumor and antitumor effects. Tumor-specific antibodies derived from B cells can combat tumor growth; however, humoral immunity can also recruit a microenvironment of inflammatory stromal cells that aids tumor proliferation.[3] Macrophages, NK cells, NKT cells, and myeloid-derived suppressor cells also play differential roles in tumor progression and inhibition as outlined in Fig 1.[1-6]

UV radiation-induced immunosuppression. UV radiation disrupts antigen presentation by Langerhans cells, leading to preferential stimulation of Th2 cells and proliferation of a subset of T regulatory cells (CD4+, CD25+, Foxp3+, CTLA-4+, and T regs) that cause a shift toward immunosuppression.[4] UV radiation also stimulates production of type 2, protumor cytokines including IL-10.[5] Finally, the production of reactive oxygen species and immunosuppressive cytokines in the setting of UV-induced DNA damage favors epidermal cell mutation, an immunosuppressive stromal environment, and tumor progression.

Immunosuppression and skin cancer in transplant recipients. Immunosuppression-related skin cancer is classically exemplified by solid organ transplant recipients (SOTRs) taking potent immunosuppressive therapy for life. Notably, SOTRs have a 65- to 250-fold increase in risk of squamous cell carcinoma (SCC), 10-fold increase in risk of basal cell carcinoma (BCC), 80- to 200-fold increase in risk of Kaposi sarcoma, 0 to 8-fold increase in risk of malignant melanoma, and 70-fold increase in risk of Merkel cell carcinoma.[5,7] Skin cancer makes up 40% of posttransplant malignancies,[8] and 82% of kidney transplant recipients will develop one or more skin cancers after 20 years.[9] Furthermore, compared with the general population, SOTRs develop more aggressive skin cancers with higher rates of metastasis and lower disease-specific survival rates in metastatic disease.[10,11] Allogeneic hematopoietic stem-cell transplant (HSCT) recipients likewise have an increased risk of SCC, BCC, and melanoma compared to the

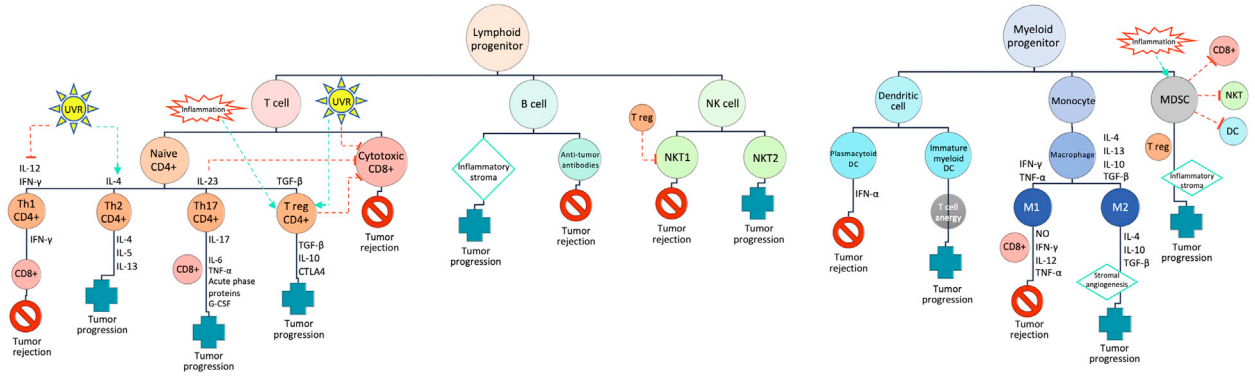

Fig 1. Antitumor and protumor actions of various immune system components. *CD*, Cluster of diffrentiation; *DC*, dendritic cell; *MDSC*, myeloid-derived suppressor cells; *Th1*, T helper type 1; *UVR*, ultraviolet radiation.

general population. While the risk of SCC is smaller in HSCT recipients compared to renal transplant recipients, HSCT recipients have been found to have a 3-fold higher risk of melanoma compared to renal transplant recipients.[12]

Overall, adding more immunosuppressive agents, increasing dosages, and extending treatment durations lead to higher risk of nonmelanoma skin cancer (NMSC).[7,13] Recently, a shift toward combined low-dose immunosuppressive regimens rather than high-dose therapy with fewer agents has been found to minimize immunosuppression-related toxicities while maintaining efficacy posttransplant.[14-17]

Immunosuppressant strength versus skin cancer risk. Customarily, the "strength" of each immunosuppressant is determined by the associated risk of infection. In the COVID era, risk categories for drugs commonly used in dermatology have been proposed and are summarized in Table I.[18]

Notably, the relative risk of skin cancer from each immunosuppressant does not directly correspond to the relative risk of infection. This discrepancy may be explained in part by the contrasting roles of immune system components in cancer surveillance versus tumor progression (Fig 1). Additionally, certain drugs have tumorigenic or antiproliferative effects independent of the immune system. For example, while systemic steroids carry a greater risk of infection, cyclosporine has a stronger association with skin cancer due to stimulation of additional carcinogenic pathways.[6,19,20] Thus, the well-known association between "immunosuppression" and skin cancer cannot be generalized; risk is highly dependent upon the source. A thorough evaluation of individual agents is key for accurately assessing individual risk.

This two-part review will focus on skin cancer risk from drugs classified as immunosuppressive. In Part I, we discuss the agents commonly used for immunosuppression in SOTRs—systemic calcineurin inhibitors (CNIs), thiopurines, inosine monophosphate dehydrogenase (IMDH) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and systemic corticosteroids—and we extend recommendations to nontransplant patients. In Part II, we assess potential indications for skin cancer screening with methotrexate, alkylating agents, biologics, and small molecule inhibitors. Additional agents such as apremilast, dupilumab, hydroxychloroquine, and dapsone are effective in calming immune-mediated processes with very little evidence suggesting increased risk of skin cancer. However, as these are not considered immunosuppressive, they are not included in this review.

Table I. Infection risk categories of immunosuppressive and immunomodulatory drugs in the COVID era[18]

Drugs commonly used in dermatologic immune-mediated diseases	Associated infection risk
Systemic steroids	high
Rituximab, cyclosporine, azathioprine, mycophenolate mofetil, JAK inhibitors, TNF inhibitors	moderate
IL-17 inhibitors, methotrexate, IL-12/23 inhibitor, IL-23 inhibitors	low
Apremilast, dupilumab, hydroxychloroquine, immunomodulators (retinoids, dapsone, colchicine)	not immunosuppressive

IL, Interleukin; *JAK*, Janus kinase; *TNF*, tumor necrosis factor.

RELATIVE RISK OF MELANOMA AND NMSC BY IMMUNOSUPPRESSANT CLASS

Key points

- Systemic CNIs and thiopurines significantly increase risk of NMSC, particularly at doses used in SOTRs.
- IMDH inhibitors and mTOR inhibitors may offer beneficial effects on skin cancer risk in SOTRs.
- Systemic corticosteroids may increase skin cancer risk in patients exposed to numerous or extended courses.

Systemic calcineurin inhibitors. Of the immunosuppressive drug classes, systemic CNIs including cyclosporine and tacrolimus have the strongest reported link to skin cancer. Mechanisms include inhibition of Langerhans cells and dermal dendritic cells, and thus decreased cytotoxic T-cell activation.[21,22] Beyond immunosuppressive effects, cyclosporine has also been shown to promote skin carcinogenesis through downregulation of PTEN (phosphatase and tensin homolog) and resultant activation of AKT (protein kinase B).[19] Calcineurin inhibition further induces ATF3 (activating transcription factor 3), leading to suppression of cancer cell senescence by p53 (tumor protein P53).[20] In addition to the large role of CNIs in posttransplant immunosuppression, cyclosporine is approved for psoriasis and commonly used off-label for rapid action in immune-mediated diseases. Tacrolimus is also frequently used off-label for chronic immunosuppression.

The link between systemic CNIs and skin cancer risk has been well-characterized in SOTRs, with data indicating a dose-dependent effect.[13] Risk of SCC in renal transplant recipients nearly tripled with cyclosporine, azathioprine, and prednisolone compared to azathioprine and prednisolone alone.[7] Using systemic tacrolimus in place of cyclosporine following renal or cardiac transplant did not significantly alter skin cancer risk in 2 clinical trials and a large case-control study.[23-25] For uses other than antirejection, the effect of systemic CNIs on skin cancer risk is less clear. A substantial increase in risk of NMSC has been shown among psoralen and ultraviolet A (PUVA)-exposed psoriasis patients treated with cyclosporine. Marcil and Stern reported a 7-fold increased incidence of SCC after first use of cyclosporine in psoriasis patients previously exposed to PUVA, equivalent to the risk from at least 200 PUVA treatments.[26]

Due to the known carcinogenic risks among other toxicities of CNIs, dermatology associations worldwide have issued clinical practice guidelines for safe cyclosporine use in the treatment of psoriasis. The American Academy of Dermatology recommends an initial dose of 2.5 mg/kg/d, divided into 2 doses, and a maximum of 5 mg/kg/d for severe cases requiring a rapid response or for those not responding after 4 to 6 weeks of therapy. Continuous cyclosporine use should not exceed 1 year in duration, although guidelines in Europe extend the limit to 2 years. Generally, guidelines favor intermittent, short-term intervals (8-16 weeks) for severe psoriasis flares, particularly in erythrodermic psoriasis or generalized pustular psoriasis.[27] This contrasts with common practice for SOTRs, who typically take 14 to 18 mg/kg prior to transplant, followed by 5 to 15 mg/kg/d for 1 to 2 weeks, then a gradual reduction to 5 to 10 mg/kg/d indefinitely.[28]

When adhering to guidelines for limited use as for psoriasis, recent evidence suggests that the risk of skin cancer may be minimized. In a large review of 60 studies on cyclosporine use for dermatologic diseases, the authors found no reported skin cancers with 6 months of continuous therapy or up to 2 years of intermittent therapy at appropriate doses. In the studies that did link cyclosporine use to skin cancer, there was typically deviation from appropriate use guidelines or inclusion of patients with substantial risk factors prior to treatment.[29]

Thus, when initiating a CNI, we recommend appropriate caution be taken with dosage, length of use, and patient eligibility. In rare cases for which no adequate alternative is available, and the risk of discontinuing therapy far outweighs potential toxicities, clinical judgment should guide further treatment with cyclosporine. Patients exposed to cyclosporine out of proportion to dermatologic guidelines (over 12 months of continuous cyclosporine therapy, over 2 years of intermittent therapy, or doses exceeding 5 mg/kg/d), those with significant preexisting risk factors including additional immunosuppressant use, and all patients reporting a history of excessive CNI use for other conditions may benefit from routine skin cancer screening.

Thiopurines. Thiopurines are antimetabolites that block purine synthesis. Azathioprine suppresses immune function by inducing apoptosis of activated T cells, decreasing antibody production, and decreasing secretion of IL-2 via its metabolites.[30-32] Azathioprine is well-established as an adjunctive antirejection therapy for renal transplant recipients. At lower doses, it is Food and Drug Administration-approved for rheumatoid arthritis and widely used in inflammatory bowel disease (IBD), ANCA (antineutrophil cytoplasmic antibodies)-associated vasculitis, and numerous other inflammatory diseases.

For SOTRs, the skin cancer risk associated with combined azathioprine and prednisolone therapy is comparable to that with cyclosporine monotherapy. In a randomized control trial of renal transplant recipients with 20 years follow-up, no difference in NMSC or melanoma risk was found between groups treated with azathioprine and prednisolone, cyclosporine monotherapy, or cyclosporine monotherapy with a switch to azathioprine and prednisolone after 3 months.[33] A meta-analysis has further substantiated the increased risk of SCC with azathioprine treatment in SOTRs.[34]

Notably, lower-dose azathioprine regimens for inflammatory conditions such as immunobullous dermatoses and connective tissue diseases may also confer an increased risk of skin cancer.[35-38] Three large cohort studies demonstrated a significant link between thiopurine use for IBD and risk of NMSC.[35-37] Peyrin-Biroulet et al[35] reported a 6-fold increase in risk of NMSC with ongoing thiopurine therapy and 4-fold increase with past exposure. The authors suggested lifelong skin cancer screening for IBD patients treated with thiopurines based on these results. Similarly, Kopylov et al[37] found the risk of NMSC significantly elevated after 5 years of thiopurine therapy for IBD (odds ratio [OR], 1.78). The association was also upheld for patients with ANCA-associated vasculitis on azathioprine therapy.[38]

Given the risk associated with long-term thiopurine use, routine skin cancer surveillance may be indicated for patients who have received thiopurine therapy for any inflammatory conditions for 5 or more years.

IMDH inhibitors. IMDH inhibitors such as mycophenolate mofetil (MMF) deplete guanosine nucleotides in lymphocytes, reducing lymphocyte proliferation and suppressing cell-mediated and humoral immunity. Additional mechanisms include inhibition of lymphocyte and monocyte adhesion and reduced nitric oxide production.[39] They are primarily used as antirejection agents following solid organ transplant. However, like azathioprine, mycophenolate is also frequently used in a wide range of rheumatic and inflammatory diseases including immunobullous dermatoses and connective tissue diseases.

Data from SOTRs strongly suggest a lower risk of SCC with mycophenolate therapy, particularly compared with azathioprine. A cohort study of lung transplant recipients found a 76% lower cutaneous SCC risk in patients who switched from azathioprine to MMF compared with those who continued azathioprine.[40] Similarly, in a case control study of renal and cardiac transplant recipients, those who ever used mycophenolate had a significantly reduced incidence of SCC compared with those who never received mycophenolate (OR, 0.45). An inverse relationship between mycophenolate and SCC was upheld even when controlling for azathioprine and tacrolimus use.[25] Finally, in a cohort of cardiac transplant recipients, mycophenolate use was found to be a protective factor against SCC (relative risk, 0.3).[41]

There are insufficient data for nontransplant patients taking mycophenolate for autoimmune and inflammatory diseases to comment on skin cancer screening practices in these patients. Overall, however, current evidence does not suggest a need for heightened skin cancer screening due to use of this agent alone.

mTOR inhibitors. mTOR inhibitors, including sirolimus, everolimus, and temsirolimus, have both immunosuppressive and antiproliferative effects. Following antigen binding to a T-cell receptor with CD28 co-stimulation, or in response to IL-2 receptor binding, the activated mTOR pathway leads to increased protein translation for cell division. By interfering with mTOR complex formation, mTOR inhibitors prevent T cells from entering the S phase of the cell cycle and induce anergy in naïve T cells.[42] They are useful for rejection prophylaxis following organ transplant, malignancies such as renal cell carcinoma and transplant-related Kaposi sarcoma, and other proliferative disorders including tuberous sclerosis. Evidence is also growing for a role of mTOR inhibitors in psoriasis.[43]

Given their antiproliferative and antineoplastic actions, mTOR inhibitors offer a beneficial alternative for SOTRs at high risk for skin cancer. Compared to a traditional transplant regimen of a CNI, azathioprine, and/or MMF, switching one or more of these agents to an mTOR inhibitor significantly reduced the incidence of SCC in 4 randomized prospective trials for sirolimus and 2 observational studies that included everolimus.[44-49]

However, not all studies have found a significant reduction in skin cancer risk with mTOR inhibitors. Inconsistent results may be explained in part by the control regimen used. A difference in risk is less likely to be found when comparing an mTOR inhibitor to an MMF-based regimen.[50] On the other hand, switching from or reducing a CNI when starting an mTOR inhibitor may yield a stronger effect.[51]

For nontransplant patients using mTOR inhibitors, insufficient data exist to assess skin cancer risk. However, given the antiproliferative mechanisms of mTOR inhibitors, the reduction in SCC in SOTRs after switching to mTOR inhibitors and the efficacy of mTOR inhibitors in the treatment of malignancies including Kaposi sarcoma, the evidence suggests a

potential net protective effect despite immunosuppression. Thus, we do not suspect a beneficial role of heightened skin cancer screening solely due to mTOR inhibitor use in nontransplant patients without additional risk factors.

Systemic corticosteroids. Systemic corticosteroids are paramount in the management of acute inflammation in countless disease processes. Specifically, glucocorticoids are well-known for their ability to block leukocyte transmigration, resulting in neutrophilic leukocytosis and reduced inflammatory activity at sites of infection and injury. Glucocorticoids also decrease the production of inflammatory cytokines and disrupt macrophage functioning. At high doses, they deplete T cells and inhibit production of type 1 and type 2 cytokines by activated T cells. Of note, the suppression of Th1 outweighs that of Th2, resulting in a relative shift toward Th2, thus an overall protumor effect.[52]

Posttransplant immunosuppression relies heavily on corticosteroids in conjunction with other agents such as cyclosporine, azathioprine, and/or mycophenolate. Overall, these regimens elevate the risk of NMSC in transplant recipients compared to the general population. However, the degree to which corticosteroids contribute to this risk is unclear, as standard of care indicates combination therapy.

In nontransplant patients, available evidence suggests a modest link between systemic glucocorticoid use and NMSC incidence, especially with greater glucocorticoid exposure. One large case-control study reported significantly higher odds of SCC (OR, 2.31) and BCC (OR, 1.49) in patients taking oral glucocorticoids for 1 month or longer.[53] Another case-control study found a slight elevation in incidence of BCC in glucocorticoid users; associations for SCC, malignant melanoma, and non-Hodgkin lymphoma were nonsignificant.[54] Not all studies have corroborated a link between glucocorticoid use and BCC or SCC.[55] However, results seem heavily influenced by the degree of exposure. Upon stratification by number of glucocorticoid prescriptions, Sørensen et al found a 2.5-fold increase in SCC and 1.5-fold increase in BCC in patients who received 15 or more prescriptions.[56]

In nontransplant patients with a history of few, infrequent, and short (less than 1 month) courses of systemic corticosteroids, there is very little evidence to warrant screening solely due to steroid use. Patients who may benefit from heightened surveillance include those with a history of numerous courses (over 10-15) and/or extended periods (several months or more) of systemic corticosteroid therapy. History should also be carefully reviewed in these patients for coexisting risk factors that may have an additive effect or otherwise obviate the need for screening. The risks of skin cancer with the above therapies are summarized in Table II.

RECOMMENDATIONS

Key points

- Current guidelines recommend regular skin cancer screening for all SOTRs irrespective of immunosuppressive regimen.
- Dermatologists should consider specific posttransplant immunosuppressive agents in an overall risk assessment for each patient to guide frequency of screenings.
- Nontransplant patients exposed to high levels of calcineurin inhibitors, thiopurines, and systemic corticosteroids may benefit from routine skin cancer screening.
- Prescribing practices should be aimed at minimizing exposure to high-risk immunosuppressants whenever feasible.

Skin cancer screening in posttransplant immunosuppression. After solid organ transplant, guidelines for initial skin cancer screening have been established by Delphi consensus. Full-body skin examination should be performed for high-risk Caucasian patients within 2 years after transplant, and all Caucasian, Asian, Hispanic, and high-risk African American patients within 5 years after transplant. The high-risk category includes thoracic organ recipients, recipients aged 50 and older, male recipients, and those with previous strong and protracted UV exposure, additional immunosuppressant use, or prior skin cancer.[57]

Following initial screening, patients should continue with regular skin exams at intervals determined on an individual basis. There are no conclusive guidelines for subsequent follow-up, although recommendations have been published and are summarized in Table III.[58] Due to wide variation in skin cancer risk associated with different posttransplant immunosuppressants, dermatologists should consider the specific regimen of the transplant recipient in overall risk assessment for frequency of screenings. Identifying drug risk is most useful for transplant patients with no history of skin cancer and no other major risk factors. For example, if taking low-risk agents such as mycophenolate or mTOR inhibitors, skin exams may be safely spaced further apart in these patients.

Skin cancer screening in nontransplant immunosuppression. In addition to transplant recipients, certain non-transplant patients using high-risk immunosuppressants may benefit from

Table II. Comparison of immunosuppressants used in transplant recipients and effects on skin cancer risk

Immunosuppressant class (drug)	FDA-approved uses	Common off-label uses	Transplant dosage	Nontransplant dosage	Transplant NMSC risk	Nontransplant NMSC risk	Melanoma risk	Highest level of evidence
Calcineurin inhibitor								
Cyclosporine (C)	Organ transplant, psoriasis (C)	Hematologic immune diseases, GVHD, FSGS, MG, leukemia, IBD, uveitis, RA	4-12 mg/kg/d, indefinitely (C)	1-4 mg/kg/d, short-term (C)	+++*	+	+/−	IA
Tacrolimus (T)			0.1-0.2 mg/kg/d, indefinitely (T)	0.2 mg/kg/d, short-term (T)2-5 mg/d, long-term (T)				
Thiopurine								
Azathioprine	Kidney transplant, RA	Behcet, BP, IBD, DM/PM, vasculitis, autoimmune renal, lung, liver, and hematologic diseases, MG, pemphigus vulgaris and foliaceus, sarcoidosis, uveitis	1-3 mg/kg/d	0.5-2.5 mg/kg/d	+++*	++	+/−	IA
IMDH inhibitor								
Mycophenolate mofetil	Organ transplant	BP, DM, CLE, GVHD, vasculitis, autoimmune renal, liver, and lung disease, IBD, MG, pemphigus vulgaris and foliaceus, systemic sclerosis, uveitis	2-3 g/d	1-3 g/d	−†	?	+/−	III
mTOR inhibitor								
Sirolimus (S) Everolimus (E)	Organ transplant, LAM (S), breast cancer (E), neuroendocrine tumors (E), RCC (E), TSC (E)	Other tumors, GVHD (S), Hodgkin lymphoma (E), Waldenstrom macroglobulinemia (E)	2-5 mg/d (S) 1.5-3 mg/d (E)	2-4 mg/d (S) 10 mg/d (E)	−†	?	+/−	IB (NMSC), IA (all other malignancy)

Continued

Table II. Cont'd

Immunosuppressant class (drug)	FDA-approved uses	Common off-label uses	Transplant dosage	Nontransplant dosage	Transplant NMSC risk	Nontransplant NMSC risk	Melanoma risk	Highest level of evidence
Systemic corticosteroid								
Prednisone	Many inflammatory and immune-mediated diseases	Additional inflammatory states	2-5 mg/d	2.5-10 mg/d (low-dose), 1-1.5 mg/kg/d (high-dose)	?	+ or +/−	+/−	IB

Degree of risk: +, small increase in risk; ++, moderate increase in risk; +++, large increase in risk; −, decreased risk; +/−, minimal or no effect on risk; ?, insufficient data.
Highest level of evidence: IA, meta-analysis of randomized controlled trials; IB, at least one randomized controlled trial; IIA, at least one controlled study without randomization; IIB, at least one other type of experimental study; III, nonexperimental descriptive studies; IV, expert committee reports/opinions or clinical experience of respected authorities.
BP, Bullous pemphigoid; *CLE*, cutaneous lupus erythematosus; *DM*, dermatomyositis; *FSGS*, focal segmental glomerulosclerosis; *GVHD*, graft-versus-host disease; *IBD*, inflammatory bowel disease; *LAM*, lymphangioleiomyomatosis; *MG*, myasthenia gravis; *PM*, polymyositis; *RA*, rheumatoid arthritis; *RCC*, renal cell carcinoma; *TSC*, tuberous sclerosis complex; *UC*, ulcerative colitis.
*Compared to no therapy.
†Compared to traditional transplant regimens.

Table III. Suggested follow-up intervals for skin cancer screening in transplant recipients based on skin cancer history[58]

Patient history	Suggested screening interval
No history of skin cancer or AK	Yearly for high-risk patients, less frequently for lower-risk patients
History of AK or one low-risk NMSC	Every 6 mo
Multiple NMSCs or a history of a high-risk SCC	Every 3 mo
History of pretransplant melanoma or melanoma in situ	Every 6 mo
Post-transplant melanoma	Every 3 mo for 2 y, then at least every 6 mo
Rapidly developing tumors, aggressive tumors, or metastatic skin cancer	Every 4 to 6 wk
Any history	Skin self-examination should be performed monthly.

AK, Actinic keratosis; *NMSC*, nonmelanoma skin cancer.

Table IV. Recommended nontransplant patients to receive routine skin cancer screening based on use of select immunosuppressants

Immunosuppressant shown to increase skin cancer risk	Patients to screen
Systemic calcineurin inhibitors	Screen patients who have received over 12 mo of continuous exposure or over 2 y of intermittent exposure to a calcineurin inhibitor, patients taking cyclosporine at doses over 5 mg/kg/d, and patients with significant preexisting risk factors including additional immunosuppressant use.
Thiopurines	Screen patients exposed to a thiopurine for 5 or more y.
Systemic corticosteroids	Consider screening for patients with a history of numerous courses (over 10-15), extended exposure (several months or more), and/or significant additional immunosuppressant use.

routine skin cancer screening. Our recommendations are summarized in Table IV.

Recommendations for minimizing high-risk immunosuppressant use. Finally, we emphasize prescribing practices aimed at minimizing overall

exposure to high-risk medications. For CNIs, thiopurines, and systemic steroids, use the lowest effective dose for the shortest duration necessary. When greater potency or duration of therapy is required, certain combined low-dose regimens may be preferable than high dose of a single agent.

Conflicts of interest

None disclosed.

REFERENCES

1. Ostrand-Rosenberg S. Immune surveillance: a balance between protumor and antitumor immunity. *Curr Opin Genet Dev*. 2008;18(1):11-18. https://doi.org/10.1016/j.gde.2007.12.007
2. Langowski JL, Zhang X, Wu L, et al. IL-23 promotes tumour incidence and growth. *Nature*. 2006;442:461-465.
3. de Visser KE, Korets LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. *Cancer Cell*. 2005;7:411-423.
4. Yu SH, Bordeaux JS, Baron ED. The immune system and skin cancer. *Adv Exp Med Biol*. 2014;810:182-191. https://doi.org/10.1007/978-1-4939-0437-2_10
5. Rangwala S, Tsai KY. Roles of the immune system in skin cancer. *Br J Dermatol*. 2011;165(5):953-965. https://doi.org/10.1111/j.1365-2133.2011.10507.x
6. Rabinovich BA, Li J, Shannon J, et al. Activated, but not resting, T cells can be recognized and killed by syngeneic NK cells. *J Immunol*. 2003;170(7):3572-3576.
7. Jensen P, Hansen S, Møller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol*. 1999;40(2 Pt 1):177-186. https://doi.org/10.1016/s0190-9622(99)70185-4
8. Penn I. Post-transplant malignancy: the role of immunosuppression. *Drug Saf*. 2000;23:101-113.
9. Ramsay HM, Fryer AA, Hawley CM, et al. Non-melanoma skin cancer risk in the Queensland renal transplant population. *Br J Dermatol*. 2002;147:950-956.
10. Lott DG, Manz R, Koch C, et al. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. *Transplantation*. 2010;90:683-687.
11. Martinez JC, Otley CC, Stasko T, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. *Arch Dermatol*. 2003;139(3):301-306. https://doi.org/10.1001/archderm.139.3.301
12. Omland SH, Gniadecki R, Hædersdal M, Helweg-Larsen J, Omland LH. Skin cancer risk in hematopoietic stem-cell transplant recipients compared with background population and renal transplant recipients: a population-based cohort study. *JAMA Dermatol*. 2016;152(2):177-183. https://doi.org/10.1001/jamadermatol.2015.3902
13. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet*. 1998;351(9103):623-628. https://doi.org/10.1016/S0140-6736(97)08496-1
14. Benazzo A, Cho A, Nechay A, et al. Combined low-dose everolimus and low-dose tacrolimus after alemtuzumab induction therapy: a randomized prospective trial in lung transplantation. *Trials*. 2021;22(1):6. https://doi.org/10.1186/s13063-020-04843-9
15. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357(25):2562-2575. https://doi.org/10.1056/NEJMoa067411
16. Gökler J, Aliabadi-Zuckermann A, Zuckermann A, et al. Extracorporeal photopheresis with low-dose immunosuppression in high-risk heart transplant patients-A pilot study. *Transpl Int*. 2022;35:10320. https://doi.org/10.3389/ti.2022.10320
17. Pascual J, Berger SP, Chadban SJ, et al. Evidence-based practice: guidance for using everolimus in combination with low-exposure calcineurin inhibitors as initial immunosuppression in kidney transplant patients. *Transpl Rev (Orlando)*. 2019;33(4):191-199. https://doi.org/10.1016/j.trre.2019.07.001
18. Zahedi Niaki O, Anadkat MJ, Chen ST, et al. Navigating immunosuppression in a pandemic: a guide for the dermatologist from the COVID Task Force of the Medical Dermatology Society and Society of Dermatology Hospitalists. *J Am Acad Dermatol*. 2020;83(4):1150-1159. https://doi.org/10.1016/j.jaad.2020.06.051
19. Han W, Ming M, He TC, He YY. Immunosuppressive cyclosporin A activates AKT in keratinocytes through PTEN suppression: implications in skin carcinogenesis. *J Biol Chem*. 2010;285(15):11369-11377. https://doi.org/10.1074/jbc.M109.028142
20. Wu X, Nguyen BC, Dziunycz P, et al. Opposing roles for calcineurin and ATF3 in squamous skin cancer. *Nature*. 2010;465(7296):368-372. https://doi.org/10.1038/nature08996
21. Dupuy P, Bagot M, Michel L, et al. Cyclosporin A inhibits the antigen-presenting functions of freshly isolated human Langerhans cells in vitro. *J Invest Dermatol*. 1991;96:408-413.
22. Sauma D, Fierro A, Mora JR, et al. Cyclosporine preconditions dendritic cells during differentiation and reduces IL-2 and IL-12 production following activation: a potential tolerogenic effect. *Transpl Proc*. 2003;35:2515-2517.
23. Gaber AO, Kahan BD, Van Buren C, et al. Comparison of sirolimus plus tacrolimus versus sirolimus plus cyclosporine in high-risk renal allograft recipients: results from an open-label, randomized trial. *Transplantation*. 2008;86(9):1187-1195. https://doi.org/10.1097/TP.0b013e318187bab0
24. Silva HT Jr, Yang HC, Meier-Kriesche HU, et al. Long-term follow-up of a phase III clinical trial comparing tacrolimus extended-release/MMF, tacrolimus/MMF, and cyclosporine/MMF in de novo kidney transplant recipients. *Transplantation*. 2014;97(6):636-641. https://doi.org/10.1097/01.TP.0000437669.93963.8E
25. Coghill AE, Johnson LG, Berg D, Resler AJ, Leca N, Madeleine MM. Immunosuppressive medications and squamous cell skin carcinoma: nested case-control study within the skin cancer after organ transplant (SCOT) cohort. *Am J Transpl*. 2016;16(2):565-573. https://doi.org/10.1111/ajt.13596
26. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet*. 2001;358(9287):1042-1045. https://doi.org/10.1016/S0140-6736(01)06179-7
27. Soleymani T, Vassantachart JM, Wu JJ. Comparison of guidelines for the use of cyclosporine for psoriasis: a critical appraisal and comprehensive review. *J Drugs Dermatol*. 2016;15(3):293-301.
28. Tapia C, Nessel TA, Zito PM. Cyclosporine. In: *StatPearls*. StatPearls Publishing; 2021.
29. Muellenhoff MW, Koo JY. Cyclosporine and skin cancer: an international dermatologic perspective over 25 years of experience. A comprehensive review and pursuit to define safe use of cyclosporine in dermatology. *J Dermatolog Treat*. 2012;23(4):290-304. https://doi.org/10.3109/09546634.2011.590792
30. Trotter JL, Rodey GE, Gebel HM. Azathioprine decreases suppressor T cells in patients with multiple sclerosis. *N Engl*

J Med. 1982;306(6):365-366. https://doi.org/10.1056/NEJM198202113060614
31. Bacon PA, Salmon M. Modes of action of second-line agents. *Scand J Rheumatol Suppl*. 1987;64:17-24. https://doi.org/10.3109/03009748709096717
32. Tiede I, Fritz G, Strand S, et al. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J Clin Invest*. 2003;111(8):1133-1145. https://doi.org/10.1172/JCI16432
33. Gallagher MP, Kelly PJ, Jardine M, et al. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *J Am Soc Nephrol*. 2010;21(5):852-858. https://doi.org/10.1681/ASN.2009101043
34. 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 Transpl*. 2016;16(12):3490-3503. https://doi.org/10.1111/ajt.13863
35. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology*. 2011;141(5):1621-1628.e1-5. https://doi.org/10.1053/j.gastro.2011.06.050
36. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012;143(2):390-399.e1. https://doi.org/10.1053/j.gastro.2012.05.004
37. Kopylov U, Vutcovici M, Kezouh A, Seidman E, Bitton A, Afif W. Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec Claims Database Study. *Inflamm Bowel Dis*. 2015;21(8):1847-1853. https://doi.org/10.1097/MIB.0000000000000457
38. van Daalen EE, Rizzo R, Kronbichler A, et al. Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. *Ann Rheum Dis*. 2017;76(6):1064-1069. https://doi.org/10.1136/annrheumdis-2016-209925
39. Allison AC. Mechanisms of action of mycophenolate mofetil. *Lupus*. 2005;14(Suppl 1):s2-s8. https://doi.org/10.1191/0961203305lu2109oa
40. Vos M, Plasmeijer EI, van Bemmel BC, et al. Azathioprine to mycophenolate mofetil transition and risk of squamous cell carcinoma after lung transplantation. *J Heart Lung Transpl*. 2018;37(7):853-859. https://doi.org/10.1016/j.healun.2018.03.012
41. Molina BD, Leiro MG, Pulpón LA, et al. Incidence and risk factors for nonmelanoma skin cancer after heart transplantation. *Transpl Proc*. 2010;42(8):3001-3005. https://doi.org/10.1016/j.transproceed.2010.08.003
42. McMahon G, Weir MR, Li XC, Mandelbrot DA. The evolving role of mTOR inhibition in transplantation tolerance. *J Am Soc Nephrol*. 2011;22(3):408-415. https://doi.org/10.1681/ASN.2010040351
43. Karagianni F, Pavlidis A, Malakou LS, Piperi C, Papadavid E. Predominant role of mTOR signaling in skin diseases with therapeutic potential. *Int J Mol Sci*. 2022;23(3):1693. https://doi.org/10.3390/ijms23031693
44. Alberú J, Pascoe MD, Campistol JM, et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation*. 2011;92(3):303-310. https://doi.org/10.1097/TP.0b013e3182247ae2
45. Salgo R, Gossmann J, Schöfer H, et al. Switch to a sirolimus-based immunosuppression in long-term renal transplant recipients: reduced rate of (pre-)malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. *Am J Transpl*. 2010;10(6):1385-1393. https://doi.org/10.1111/j.1600-6143.2009.02997.x
46. Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. *Am J Transpl*. 2012;12(5):1146-1156. https://doi.org/10.1111/j.1600-6143.2012.04004.x
47. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol*. 2013;31(10):1317-1323. https://doi.org/10.1200/JCO.2012.45.6376
48. Euvrard S, Boissonnat P, Roussoulières A, et al. Effect of everolimus on skin cancers in calcineurin inhibitor-treated heart transplant recipients. *Transpl Int*. 2010;23(8):855-857. https://doi.org/10.1111/j.1432-2277.2009.01010.x
49. Alter M, Satzger I, Schrem H, Kaltenborn A, Kapp A, Gutzmer R. Non-melanoma skin cancer is reduced after switch of immunosuppression to mTOR-inhibitors in organ transplant recipients. *J Dtsch Dermatol Ges*. 2014;12(6):480-488. https://doi.org/10.1111/ddg.12355
50. Gräger N, Leffler M, Gottlieb J, et al. Risk factors for developing nonmelanoma skin cancer after lung transplantation. *J Skin Cancer*. 2019;2019:7089482. https://doi.org/10.1155/2019/7089482
51. Ying T, Wong G, Lim W, et al. De novo or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: a trial-based linkage study. *Am J Transpl*. 2018;18(12):2977-2986. https://doi.org/10.1111/ajt.14948
52. Franchimont D, Louis E, Dewe W, et al. Effects of dexamethasone on the profile of cytokine secretion in human whole blood cell cultures. *Regul Pept*. 1998;73(1):59.
53. Karagas MR, Cushing GL Jr, Greenberg ER, Mott LA, Spencer SK, Nierenberg DW. Non-melanoma skin cancers and glucocorticoid therapy. *Br J Cancer*. 2001;85(5):683-686. https://doi.org/10.1054/bjoc.2001.1931
54. Jensen AØ, Thomsen HF, Engebjerg MC, et al. Use of oral glucocorticoids and risk of skin cancer and non-Hodgkin's lymphoma: a population-based case-control study. *Br J Cancer*. 2009;100(1):200-205. https://doi.org/10.1038/sj.bjc.6604796
55. Baibergenova AT, Weinstock MA, VATTC Trial Group. Oral prednisone use and risk of keratinocyte carcinoma in non-transplant population. The VATTC trial. *J Eur Acad Dermatol Venereol*. 2012;26(9):1109-1115. https://doi.org/10.1111/j.1468-3083.2011.04226.x
56. Sørensen HT, Mellemkjaer L, Nielsen GL, Baron JA, Olsen JH, Karagas MR. Skin cancers and non-hodgkin lymphoma among users of systemic glucocorticoids: a population-based cohort study. *J Natl Cancer Inst*. 2004;96(9):709-711. https://doi.org/10.1093/jnci/djh118
57. Crow LD, Jambusaria-Pahlajani A, Chung CL, et al. Initial skin cancer screening for solid organ transplant recipients in the United States: delphi method development of expert consensus guidelines. *Transpl Int*. 2019;32(12):1268-1276. https://doi.org/10.1111/tri.13520
58. Stasko T, Hanlon AM. Prevention and Management of Skin Cancer in Solid Organ Transplant Recipients. Uptodate; 2022.