Published in final edited form as:
J Am Acad Dermatol. 2014 August ; 71(2): 359–365. doi:10.1016/j.jaad.2014.02.039.

Skin cancer in organ transplant recipients: more than the immune system

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Abstract

Organ transplant recipients (OTRs) are at increased risk of developing non-melanoma skin cancers (NMSC). This has long been thought to be due to immunosuppression and viral infection. However, skin cancer risk among individuals with AIDS or iatrogenic immunodeficiency does not approach the levels seen in OTRs, suggesting other factors play a critical role in oncogenesis. In clinical trials of OTRs, switching from calcineurin inhibitors to mammalian Target of Rapamycin (mTOR) inhibitors consistently led to a significant reduction in the risk of developing new skin cancers. New evidence suggests calcineurin inhibitors interfere with p53 signaling and nucleotide excision repair. These two pathways are associated with NMSC, and squamous cell carcinoma (SCC) in particular. This finding may help explain the predominance of SCC over basal cell carcinoma in this population. mTOR inhibitors do not appear to impact these pathways. Immunosuppression, viral infection, and impaired DNA repair and p53 signaling all interact in OTRs to create a phenotype of extreme risk for NMSC.

Introduction

The extreme risk of non-melanoma skin cancer (NMSC) among organ transplant recipients (OTRs) is well-known[1–6]. Because of risks reported to be increased twenty to one hundred-fold, the dogma has become that immunosuppression is a risk factor for NMSC[7,8]. Recent findings suggest, however, there is more to the risk of NMSC in OTRs than just immunosuppression[9–11]. Several recent reviews have expertly summarized individual topics in article, but have not examined the risk factors as they interact in OTRs to contribute to the elevated NMSC risk[9–14]. This review aims to synthesize the epidemiological, clinical, and basic science evidence that suggest that immunosuppression by itself is not the cause of the extreme risk of NMSC, but rather the combination of immunosuppression, viral infection,

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Conflict of interest: The authors have no conflicts of interest to declare

and the mechanism of action of the immunosuppressive medications all contribute to the risk of skin cancer in OTRs.

Skin cancer in organ transplant recipients

OTRs are at extreme risk for NMSC, with many institutions devoting specialty clinics to the care of this population[1,2,9]. For example, a population-based study in Sweden observed a standardized incidence ratio (SIR) of 121 (95% confidence interval (CI) 116–127) among OTRs compared to the general population[15]. A multi-ethnic cohort in the UK observed a 26% 10-year incidence of NMSC in OTRs, and a 15% incidence among those of African ancestry, a group that otherwise would be at low risk of ultraviolet radiation (UVR) induced cancers[16]. The lower incidence among those with darker pigmentation suggests that UVR still plays a significant role in the development of these cancers. Fitzpatrick skin type and sun exposure are independently associated with skin cancer risk among OTRs[9,17,18].

The paradigm has been that the immunosuppression required to keep the body from rejecting the transplanted organ also impairs immune surveillance, thereby allowing tumor cells to proliferate unchecked[7]. The fact that cumulative dosage of cyclosporine and other immunosuppressants is independently associated with risk of non-cutaneous cancers in OTRs tends to support this theory[19,20]. The best example of the association between immunosuppression and increased skin cancer risk comes from patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).

Skin cancer in HIV and AIDS patients

The role of the immune system in cancer prevention is highlighted by the increased cancer risk among AIDS patients, particularly among cancers caused by infectious agents[12]. A meta-analysis showed that compared to the general population, the SIR of Kaposi's sarcoma among OTRs was 208 (95% CI 114–349), while among AIDS patients it was 3640 (95% CI 3326–3976)[12]. The risks of cervical cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and liver cancer, all of which have known viral etiologic contributions, were greater among AIDS patients than OTRs. The lower incidence of AIDS-defining cancers among OTRs suggests greater residual immune function than in individuals with AIDS. It therefore seems logical that greater immune function should translate into a lesser risk of virally-mediated neoplasia[12]. Viral effects aside, if immunosuppression itself were the major contributor to NMSC risk, it would logically follow that AIDS patients would experience a greater increased risk of skin cancer than OTRs[12]. This was not observed. Rather, the risk of NMSC among AIDS patients was 4.11 (95% CI 1.08 – 16.6), while among OTRs it was 28.62 (95% CI 9.39 – 87.2).

In another study, HIV patients developed NMSC at an adjusted rate ratio of 2.1 (95% CI 1.9–2.3) [21]. When stratified by most recent CD4 levels, squamous cell carcinoma (SCC) risk was increased among those with CD4 <200 compared to those with >500, while there was no difference for basal cell carcinoma (BCC). As with Kaposi's sarcoma and human herpes virus-8, the stronger association between immune function and SCC could be consistent with an infectious cause, an example of which could be certain strains of human papillomavirus (HPV), which are found in a subset of SCCs[11].

Skin cancer and oncogenic viruses

The association between multiple cancers and HPV is well established[13,22,23]. The role of HPV in cutaneous SCC, as well as BCC, is less clear, although recent studies have found more significant associations[11,13,24–28]. Immunosuppressed populations have higher rates of HPV infection, and in the absence of large prospective studies, it is difficult to identify whether the immunosuppression or the viral infection is the etiologic factor[11,13,26,28]. Further clouding the picture is the stronger association between the two in those with a greater sensitivity to UVR[29]. The strongest associations between HPV and NMSC, and SCC in particular have been <4.0[29], with most others reporting point estimates to be <2.0[11,13,25,28]. The large number of HPV serotypes and differences in measuring infection have made it difficult to draw firm conclusions regarding a causal association[11,13,27,30]. As OTRs are increasingly vaccinated against HPV, it remains to be seen whether there will be a decrease in NMSC rates in this population[31]. The ongoing Skin Cancer after Organ Transplant Study will provide the first prospective evidence of HPV acquisition and association with NMSC, with results not expected for several years[32].

Merkel cell carcinoma (MCC) is caused by a polyomavirus and has a poorer prognosis in immunosuppressed patients [33,34]. Like SCC, UVR likely plays a role in the development of virally-mediated oncogenesis[35–37]. Despite OTRs commonly being infected by this virus[38], development of MCC is rare among them[9]. Immunosuppression and viral infection both contribute to NMSC in OTRs, however these factors individually or in combination do not appear to account for the extreme risks seen in OTRs[9,12,15]. Viral infection rates and NMSC in immunosuppressed non-OTRs are not known[39]. Patients with autoimmune disorders do have an increased risk of NMSC, as well as increased infection rates, but no one has yet examined both outcomes simultaneously [14,40,41]. Regardless, the NMSC risks in these patients have been well below those seen in OTRs (SIRs typically < 2.0), and do not differ significantly based on treatment[14].

Clinical trials of OTRs

In mouse models, the mammalian Target of Rapamycin (mTOR) inhibitor sirolimus has antiproliferative effects on cancer cells in addition to immunosuppressive ones[42]. It was therefore hypothesized that using sirolimus instead of calcineurin inhibitors (CNI) could potentially take advantage of both functions to lower cancer risk in OTRs[9,43]. The earliest studies used a large retrospective database of OTRs stratified by drug regimen to examine the risks of cutaneous and non-cutaneous cancer[19]. Among deceased OTRs from 1996–2001 in the United States, there were 252 NMSCs among 30,424 OTRs on cyclosporin or tacrolimus (0.83%), three individuals with a total of four NMSCs among 2,321 OTRs on CNIs or mTOR inhibitors sirolimus or everolimus (0.13%), and three NMSCs among 504 OTRs on mTOR inhibitors alone (0.60%). Although this study did not capture living OTRs, there was a significantly decreased risk of NMSC *in* both groups with any mTOR inhibitor use compared to CNI use alone.

A trial of 44 renal transplant recipients in Germany randomized patients to continue their immunosuppressive regimen, or switch to sirolimus plus 5mg daily prednisone, and

followed to track the development of new NMSC[44]. During the 12-month follow-up, eight participants withdrew due to adverse events, seven of whom were in the sirolimus group. There was a statistically significant decrease ($p = 0.0167$) in the risk of NMSC in the experimental group, as there were eight new NMSCs among the 17 on continuation therapy (47.1%), and only one among the 16 on sirolimus (6.3%). All participants in the study were sirolimus-naive; however all were stable on their regimens at time of enrollment. The most common immunosuppressant was azathioprine, although most individuals had at some point been on CNI treatment. By removing from consideration those who were unstable or otherwise failing current treatment, the data could have been enriched for OTRs who would do well on treatment, although 11 of the 16 patients on sirolimus saw an improvement in their skin by clinical assessment at 12 months, compared to no improvement in the control group and 12 of 17 rated as worse.

These findings were further explored in the CONVERT trial, in which 830 patients were randomized to switch from CNIs to an mTOR (sirolimus), and 275 were randomized to continue their CNI. At two years post conversion, the rate of skin cancers in the conversion group was less than one third that of the CNI group[45]. Another trial converted the OTRs' cyclosporine treatment to sirolimus three weeks after transplant and compared the risk of NMSC to the patients that continued on cyclosporine alone. After five years, the median time to first skin cancer was 1126 days in the group taking sirolimus versus 491 days in patients taking cyclosporine ($p=0.007$)[46].

In secondary analyses, the decreased risk was significant among only those with one previous SCC[2,47]. These findings were replicated in another multi-center trial, showing a decreased risk among those with only a single previous skin cancer[48]. This pattern of increasing risk with an increasing number of previous skin cancers is consistent with well-known patterns of UVR-induced NMSC in the general population[49]. Development of the first skin cancer in OTRs had the longest latency period before rapid accumulation of lesions[50]. The protective effect seen in this subgroup with only a single lesion could be consistent with CNIs causing a more rapid accumulation of UVR-induced damage[11,13]. For example, those with smaller amounts of chronic UV damage, as could be suggested by the presence of only a single lesion, were at lower risk of subsequent lesions after cessation of use, while those with greater amounts of UV damage, as could be suggested by multiple lesions, were at greater risk of developing subsequent lesions[49]. Some of these NMSCs may have been prevalent at baseline[51]. Molecular evidence supports this theory of diminished response to and repair of UVR-induced DNA damage[10].

In each of the trials, there was no difference in rejection rates between CNIs and mTOR inhibitors. The obvious question then becomes why are all OTRs not started on mTOR inhibitors? The reason may be that there was a considerable drop out due to severe adverse events among those on mTOR inhibitors, most frequently due to pneumonitis. While they have consistently been shown to decrease skin cancer risk, mTOR inhibitors are not without severe side effects, and patients should be encouraged to discuss the risks and benefits of these different regimens with their transplant physicians[9].

Molecular Mechanisms

A full review of the mechanisms behind the increased risk of NMSC among OTRs is beyond the scope of this review, but here we will touch on the key findings[10]. First, signaling via calcineurin and NF-AT is required for p53-mediated senescence[52]. Aberrant p53 signaling is a hallmark of SCC, and is seen in SCCs caused by UVR mutations, arsenic, and HPV[53,54]. Second, CNIs impair cells' ability to repair UVR-induced DNA damage, which is not seen in cells treated with mTOR inhibitors[10,55,56]. This attenuated repair is mediated by a decreased transcription of XPA and XPG, two components of NER and genes that harbor severe mutations that lead to Xeroderma pigmentosum[56]. There are currently conflicting data regarding impairment of XPC function [56,57]. Since up to 59% of invasive SCCs harbor a mutation in XPC as well as p53[54,58,59], it is straightforward to understand why a drug that blocks proper function of both gene products would lead to an increased risk of NMSC overall, and SCC in particular. Moreover, mTOR inhibition leads to an upregulation of Akt1 with a concomitant downregulation of Akt2[60]. UVR causes the opposite, with a decrease in Akt1 and an increase in Akt2, a pattern that is often found in SCC[60]. The fact that the two mechanisms of CNIs, interfering with both p53 and NER, are the same pathways that are altered in SCC provides an explanation for the predominance of SCC in OTRs. That mTOR inhibitors block another SCC-specific oncogenic pathway could explain why they are so effective at preventing this increased risk. More studies will be needed to understand both the mechanism of CNI on the NER and p53 pathways and its role in NMSC development.

OTRs have an increased risk of both BCC and melanoma in addition to SCC. These two other types are likely due to a similar mechanism as SCC. If CNI's impair NER function via XPA and XPG, individuals treated with these medications effectively have an induced XP phenotype[10]. That is, the inability to repair DNA lesions increases the risk for all three UV-induced skin cancers, in all skin types, as is observed in both XP and OTRs.

NER is impacted by mTOR inhibitors and other immunosuppressant drugs as well[10]. In yeast models, the transcription-coupled repair branch of NER is inhibited by sirolimus, although everolimus appears not to have a negative impact on NER in human fibroblasts. While the greatest risks appear to be associated with CNI's, individuals on other immunosuppressive regimens also experience an increased risk of NMSC. Azathioprine increases skin cancer risk to a lesser degree than CNI's, and is known to impair DNA repair[10]. Psoriasis patients on TNF-α inhibitors also have approximately a 30–75% increased risk of NMSC compared to the general population[61,62], although this risk could potentially be due to the disease itself as treatment with TNF-a inhibitors did not increase NMSC risks above other treatments[63]. Recent data suggest a potential link to NER function, as overexpression of toll-like receptor 4, which occurs in psoriasis, was inversely correlated with XPA expression and CPD removal [64]. Moreover, treatment with TNF-α inhibitors decreased DNA repair in two small studies[65,66]. Limited data exist regarding skin cancer risk associated with monotherapy using steroids or mycophenolate mofetil (MMF), although studies in mice suggest MMF has little effect [67]. While these data are compelling, most are the result of in vitro experiments in cells without viral infection or immune surveillance and so direct comparisons of their relative contributions to NMSC risk cannot be made.

Conclusions

Immunosuppression has long been known to be a risk factor for NMSC, with decreased immune surveillance hypothesized to be the etiologic factor. Large studies of patients with HIV consistently indicate an increased risk, although the magnitude of this risk is less than one tenth the risk observed in OTRs. Infection with oncogenic viruses has been suggested as a potential link between immunosuppression and NMSC. The most consistent evidence for an association between viral infection and cutaneous oncogenesis is the link between HPV and SCC. While an etiologic association would help explain the greatly increased risk of SCC among OTRs, it does not offer insight into the increased risk of BCC, for which there is less consistent evidence. Clinical trials have consistently shown a decreased risk of NMSC among those who switch to mTOR inhibitors from CNIs, initially explained by the antineoplastic effects of mTOR inhibitors. While these drugs block a crucial step along the oncogenic pathway for SCC, evidence shows that CNIs also impair NER through downregulation of several XP gene products, and also prevent p53-mediated senescence. The evidence to date suggests that decreased immune-surveillance, oncogenic viral infection, and impaired DNA repair and damage response interact to create a phenotype of extreme risk for OTRs that is not accounted for by any of these individually[30]. Future studies including each of these factors will be necessary to discern their relative contributions to NMSC risk.

Acknowledgments

Funding: This work has been supported by funding from the National Institutes of Health NIGMS grant T32GM008716 (LW)

Abbreviations

AIDS	acquired immune deficiency syndrome
BCC	basal cell carcinoma
CI	confidence interval
CNI	calcineurin inhibitor
HIV	human immunodeficiency virus
HPV	human papillomavirus
MCC	Merkel cell carcinoma
mTOR	mammalian Target of Rapamycin
NER	nucleotide excision repair
NMSC	non-melanoma skin cancer
OTR	organ transplant recipient
SCC	squamous cell carcinoma
SIR	standardized incidence ratio

UVR ultraviolet radiation

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