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Pathogenesis of Nonmelanoma Skin Cancers in Organ Transplant Recipients

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Abstract

Nonmelanoma skin cancer (NMSC) is the most common human cancer, with an incidence of more than 1.2 million per year in the U.S.A. The risk for the development of NMSCs increases by approximately 10–250 fold in chronically immune suppressed organ transplant recipients (OTRs). Solar UVB is the most common etiologic factor in the development of this neoplasm, both in immune competent and immune suppressed populations. This review provides a description of NMSC in OTRs. It also provides an account of the various immunologic and non-immune-dependent mechanisms involved in the pathogenesis and progression of NMSCs in OTRs. Finally, this review addresses possible strategies for the prevention of this cancer, particularly focusing on the aspects that may be incorporated to prevent negative effects of chemopreventive chemicals on graft survival.

Introduction

Nonmelanoma skin cancer (NMSC), the most common human cancer, has an incidence of more than 1.2 million per year in the U.S.A.. Moreover, its risk in immune suppressed populations increases by 10–250 fold. It is believed that immunosuppressive drugs create a conducive microenvironment that facilitates the unrestricted growth of cancer-initiated cells. It is also believed that, similar to immune competent individuals, the major etiologic factor for NMSC remains ultraviolet B radiation (UVB) in organ transplant recipients (OTRs). In immune competent individuals, factors such as skin color, cumulative UVB exposure, and genetic background influence tumor growth. In addition to these factors, tumor growth and aggressiveness depend on the level, type, and duration of immunosuppressive therapy, age at transplantation and type of transplanted organ in OTRs. Impairment of the body's immune functions following chronic use of immunosuppressive drugs leads to an inability to eradicate cells with precancerous changes. There are also direct carcinogenic effects of these agents on cancer-initiated cells. Skin cancer is a significant cause of morbidity and discomfort to OTRs who already suffer from numerous serious medical issues. Therefore, prevention of skin cancer in this high risk population is a major priority in these patients.

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Some of the successful chemopreventive agents tested in human skin include retinoids, cyclooxygenase inhibitors, and ornithine decarboxylase inhibitor, difluoromethylornithine (DFMO). It remains to be determined whether these agents can successfully be employed in OTRs to block skin neoplasms without damaging the graft organ. This review addresses some of these issues.

Skin Cancer

The lifetime risk for skin cancer development in the US is estimated to be 1 in 5 and greatly exceeds the incidence of all other neoplasms together [1,2]. About 1/3 of all human cancers occur in skin and more than 1.2 million new cases of non-melanoma skin cancer (NMSC) including both squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are reported annually in the US alone [1]. In addition to UVB, fair skin and age are also key risk determinants for NMSCs. Interestingly, the risk for NMSCs is further augmented in chronically immune-suppressed organ transplant recipients (OTRs).

In 2008 in the United States, about 200,000 people were living with a functioning transplanted organ or graft, another 100,000 were on the active national transplant waiting list, and 27,961 solid organ transplants were performed (See Table 1). Of all cancers that arise in OTRs, 95% are skin cancers [3]. However, the incidence of malignant melanoma, Kaposi's sarcoma, Merkel Cell tumors, cutaneous T-cell lymphoma, cutaneous B-cell lymphoma, natural killer cell lymphoma, angiosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and sebaceous carcinoma, which rarely occur in the general population, is enhanced in OTRs. Kidneys are the most frequently transplanted solid organ and, therefore, the majority of skin cancers in OTRs occur in this population (See Table 1). The risk of SCC in immunosuppressed patients is between 65- and 250-fold higher than in the general population, and the risk of BCC is 10-fold greater [4]. Analyses of Medicare claims data and the Organ Procurement and Transplant Network/United Network of Organ Sharing database have shown that the incidence of NMSC in chronically immune suppressed OTRs increases from 2.25% at 1 year to 4.95% at 2 years, and 7.43% at 3 years, and then further increases to 10–27% and 40–60% after 10 and 20 years of immune suppression respectively [5]. These patients develop NMSCs at a relatively young age with an increased risk of local recurrence, regional and distant metastasis and significant morbidity and mortality [6]. SCCs metastasize in 5–8% of transplant recipients [4]. Compared to an immune-competent population in which the ratio of BCCs/SCCs is ~3:1, the immunosuppressed population develops these neoplasms in the inverse ratio of 1:4 [7]. In addition to the factors that determine risk of NMSCs in the general population, the level, type, and duration of immunosuppressive therapy, age at transplantation and type of transplanted organ also determine the risk of skin cancer in OTRs. OTR patients at low latitudes develop a much higher incidence of skin cancer than those living at higher latitudes. Thus, in Australia 45% of OTR patients develop a NMSC within 10 years of transplantation, whereas in countries with a temperate climate (e.g. Holland, England, and Italy) the incidence is only 10–15% (Clinuvel) [8].

Immune suppression and neoplastic growth

In transplant recipients, immunosuppressive drugs severely impair the body's immune functions. Among the cell types affected are T lymphocytes, natural killer cells as well as dendritic and other antigen presenting cells. The end result is disrupted immune surveillance. As a result, a microenvironment is created that is conducive to unrestricted tumor growth. Tumors developing in chronically immune suppressed OTRs result from either transfer of neoplastic cells from donor organs or reoccurrence of primary tumors. In addition, this population is at greater risk for developing virus-induced neoplasms. This is

evidenced by the fact that the increased incidence of Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorders occurring in OTRs decreases following the withdrawal or tapering of immunosuppression. Similar results have been reported in transplant recipients infected with human herpes virus-8 (HHV-8) that develop Kaposi's sarcoma [9,10].

Skin cancers associated with human papilloma virus (HPV) infections also regress following reduction in immunosuppression. In OTRs the pathogenesis of virus infection-induced skin cancer is also significantly enhanced. For example, HPV can be found in up to 90% of cutaneous SCCs in OTRs compared to 11–32% in immunocompetent individuals [11]. In addition, cutaneous SCCs and HPV-induced warts usually co-localize in this population suggesting that these warts may progress into skin cancers. Cutaneous HPV types, the E6 oncoproteins, target Bak for proteolytic degradation. E6 protein of cutaneous HPV1 and HPV8 can also bind to XRCC1 protein which is required for the repair of single strand DNA breaks thereby impairing the efficiency of their repair. UVB-induced thymine dimers repair is also affected by E6 protein of the beta HPV5 [12]. Interestingly, certain HPVs such as the wart-associated HPV77 utilize the UVB-induced SOS-response program of the host cell to increase their own transcription activity [13]. In addition, oncogenic viruses may indirectly augment the carcinogenic response in OTRs, the description of which is beyond the scope of this review [14].

In both immune-competent and immune-suppressed populations, UVB induces photo-products in DNA that include cyclobutane dimers and (6–4) photoproducts. These lesions are potentially mutagenic and if not repaired, can lead to C to T and CC to TT transition mutations, also known as UVB “signature” mutations. These mutations occur frequently in tumor suppressor genes, oncogenes and/or other genes involved in the pathogenesis of these UV-induced skin cancers. Treatment with immunosuppressive drugs enhances the number of microscopic clones of cells overexpressing mutant p53 in renal transplant recipients [15,16]. These p53 patches are considered precursor cells for the induction of actinic keratosis and SCCs, and were found to be immunogenic in murine skin.

Immunosuppressive drugs and skin cancer pathogenesis

NMSCs behave more aggressively in chronically immunosuppressed individuals. The exact mechanism(s) by which this aggressive phenotype is achieved remains elusive. It is believed that immunosuppressive medications lead to impaired immune surveillance and failure to eradicate cells with precancerous changes. In addition, direct carcinogenic effects of these agents may also contribute to some of these effects.

Cyclosporine A (CsA) is the common immunosuppressive drug used in OTRs to prevent rejection of the transplanted organ. Additionally, CsA is also employed in the treatment of multiple diseases such as nephrotic syndrome, Crohn's disease, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, psoriasis and dermatomyositis. The risk of skin cancers in patients receiving prolonged treatment with CsA is increased. For example, patients receiving CsA-azathioprine-prednisone were found to have a 3–4.2-fold increased risk of NMSC compared to patients receiving azathioprine-prednisone alone [17,18]. In a 66 month follow-up, 60 of 231 transplant (26%) recipients receiving CsA developed cancers, 66% of which were skin cancers [19]. In a study of 488 OTRs, 10.4% receiving CsA developed a first NMSC [20]. These data together clearly indicate that CsA administration enhances skin cancer risk in humans.

CsA acts by binding to a cytoplasmic protein, cyclophilin (immunophilin) in lymphocytes, particularly T-lymphocytes. The CsA-cyclophilin complex inhibits calcineurin, which dephosphorylates the transcription factor, nuclear factor of activated T-cells (NFAT),

promoting its translocation from the cytoplasm to the nucleus. NFAT is required for the transcription of interleukin-2 (IL-2). Thus inhibition of calcineurin signaling blocks IL-2 production leading to reduced numbers of effector T-cells. In addition, blockade of NFAT signaling may also alter tumorigenesis response as discussed in detail in the proceeding section [21].

Recently, we showed that A431 SCC xenograft tumors grown in nude mice develop much faster and become much larger in size following treatment with CsA. We also showed that CsA-induced alterations are not reversible following cessation of CsA treatment and retain the inhibition of calcineurin signaling. CsA-treated tumors manifested enhanced cellular proliferation and tumor vascularity associated with high expression of vascular endothelial growth factor (VEGF). These tumors also showed increased epithelial-mesenchymal transition (EMT) and associated markers, fibronectin, α -SMA, vimentin, N-cadherin, MMP-9/-2, snail, slug, and twist with a concomitant decrease in the epithelial polarity marker E-cadherin. CsA increased transforming growth factor beta-1 (TGF β 1) expression with a concomitant increase in cell migration/invasion and a decrease in apoptosis [22]. In addition, CsA alters mitochondria-dependent cellular functions and blocks the mitochondrial permeability pore (MPP) opening, which modifies the ability of cells to undergo apoptotic cell death. We also showed that CsA-pretreated skin carcinoma cells do not respond to agents that induce apoptosis by inhibiting mitochondrial cytochrome c release, a potent pro-apoptotic stimulation factor [23].

As early as 1975, Koranda et al [24] demonstrated that treatment of hairless mice with immunosuppressive agents accelerated UVB-induced skin cancer development. They showed that 57% of immune suppressed animals developed SCCs by 139 days whereas only 18% of immune-competent mice developed these tumors after 180 days. However, no metastases were observed in the animals on chronic immune suppression regimens. Similarly, Nelson et al [25] showed that subcutaneous administration of CsA as well as azathioprine enhanced UVB-induced skin cancer development in murine models. In another study, azathioprine, prednisolone, cyclophosphamide, and CsA were found to enhance UVB-induced carcinogenesis [26]. However unlike other immunosuppressive drugs, cyclophosphamide did not enhance malignant progression,. Servilla et al [27] confirmed that CsA augments the growth of UVB-induced transplanted tumors. However, contrary to earlier observations topical CsA inhibited phorbol ester-induced cutaneous tumor promotion [28]. In further studies, these results were confirmed by Yokota et al who showed that topically administered CsA behaved differently than parenterally administered CsA with respect to its effects on tumor development [29]. Interestingly, rapamycin (sirolimus) administration while protecting against allograft rejection, also diminished tumor growth in various immune suppressed murine models [30].

Recently, Wulff et al re-investigated the effects of immunosuppressive drugs on UVB-induced skin carcinogenesis in SKH-1 hairless mice [31]. Similar to earlier reports, they also observed an enhanced tumor progression following CsA administration in UVB-irradiated animals. Moreover, tumor size in CsA-treated animals was much larger than in control animals. Rapamycin when co-administered with CsA, significantly decreased multiplicity, size and progression of benign lesions to SCCs. The augmented tumor growth in chronically immune suppressed animals was demonstrated to be related to enhanced inflammation and tumor angiogenesis [32]. Their study also showed that degree of enhancement in skin carcinogenesis by immunosuppressive agents is variable and depends upon the nature of the administered immunosuppressive drug.

O'Donovan *et al* showed that the immunosuppressive drug, azathioprine acts through a distinct mechanism to augment tumor growth. Exposure of azathioprine-treated patients to

UVA generated mutagenic adducts detectable in their skin. There was a direct correlation between adducts and the enhanced occurrence of skin cancer in these patients [33]. Dworkin et al proposed that enhanced chromosomal aberrations in UVB-induced tumorigenesis result from chronic immune suppression [34]. These studies also demonstrated the distinctive mechanisms associated with specific immunosuppressive drugs. Thus, tacrolimus treatment augments skin carcinogenesis via chromosomal aberrations whereas CsA targets an entirely different pathway. In addition, alterations in telomere length and telomerase activity were found to influence the incidence of both BCCs and SCCs in immune suppressed populations [35,36].

Vogt et al showed that treatment of *Ptch*^{+/-} mice with immunosuppressive drugs does not significantly alter their lifespan. However, they noted a 2.5 fold increase in BCC burden in CsA and prednisolone immunosuppressed animals exposed to ionizing radiation derived from a cesium-137 source [37]. Consistent with the notion that CsA enhances TGFβ1 signaling, elevated P-Smad2 levels were found to be associated with the tumors excised from OTRs [38].

Immune-dependent and non-immunologic mechanisms underlying pathogenesis of cutaneous neoplasm

The gross immunologic mechanisms related to enhancement of skin carcinogenesis in immune suppressed populations may not differ significantly with the type of immunosuppressive agent used. However, immune-independent mechanisms which usually represent the direct effects of immunosuppressive agents on cancer cells may be agent specific. Recently Wu et al [21] reported that genetic and pharmacological suppression of calcineurin/NFAT function by CsA promotes tumor development in murine skin and in xenografts in immune compromised animals. Calcineurin/NFAT inhibition counteracts p53-dependent cancer cell senescence thereby enhancing its tumorigenic potential. These authors found that ATF3, which is a member of the AP1 family, is selectively induced by calcineurin/NFAT inhibition in human and murine tumors. ATF3 suppresses p53-dependent senescence and tumorigenic potential [21]. CsA enhances AKT activation by reducing the expression of PTEN. In addition, it has been shown that CsA-mediated PTEN downregulation occurs at the transcriptional level and is dependent on epidermal growth factor [39].

Prevention of skin neoplasms in OTRs – Retinoids, Ornithine Decarboxylase, and Cyclooxygenase

Skin cancer is a significant cause of morbidity and discomfort to OTRs who already suffer from numerous serious medical issues [4–8]. Therefore, prevention of skin cancer in this high risk population is a very important issue. Chemoprevention strategies are focused on reducing and delaying the development of skin cancer in these patients. Besides sunscreens and educational aspects of skin cancer prevention, the management of cutaneous neoplasms through the use of relatively non-toxic and highly tolerable chemical agents is a primary goal of skin cancer chemoprevention programs [40,41]. In immune-competent populations, a number of agents have been found to be effective in reducing the risk of skin cancer [42]. Many of these agents are derived from dietary and herbal constituents while others are synthetic chemical compounds targeting specific proteins. Some of the synthetic agents successfully tested in humans include retinoids, cyclooxygenase inhibitors, and the ornithine decarboxylase inhibitor, difluoromethylornithine (DFMO). However, the major issue with the use of chemicals proven effective in immune-competent populations is their potential

deleterious effects on graft survival and function which needs to be evaluated before they can be recommended for trial in OTRs [43].

Retinoids have been employed in a number of human trials to block skin carcinogenesis in transplant patients [43,44]. Interestingly, these studies report a reduction in malignant and pre-malignant lesions in this population. These studies also describe an increased benefit of systemic retinoids in patient populations with a previous history of skin cancer. In this regard, acitretin proved more effective than other retinoids tested. The side effects of this treatment are observed only in a minority of patients and include cheilitis, dry skin, hair loss, elevated cholesterol and triglycerides, and thrombocytopenia. These agents are, in general, well tolerated in terms of their effects on the graft. Although graft failure/dysfunction was reported in several cases, it was not considered due to retinoid therapy. However, the major concern with the use of retinoids remains the rebound reoccurrence of skin neoplasms which is often found following discontinuation of the drug. The exact mechanism by which these agents act to block skin cancer development remains largely unknown, but retinoids are known to exert physiological effects by binding to specific nuclear receptors which belong to a super family that includes receptors for glucocorticosteroids, thyroid hormone, vitamin D, and peroxisome proliferator-activators. The two classes of retinoid nuclear receptors, retinoid nuclear receptors (RARs) and retinoid X receptors (RXRs), are encoded by distinct genes that form multiple heterodimers or homodimers and, in turn, activate ligand-dependent transcription factors for genes containing a retinoic acid response element (RARE). Interestingly, about 500 genes have been found to contain retinoid regulatory elements [43]. It remains to be determined whether this mechanism also operates in OTRs.

DFMO is an irreversible suicidal inhibitor of ornithine decarboxylase, a rate limiting enzyme in the polyamine biosynthetic pathway. Polyamines are important for cell growth and proliferation. DFMO has been shown to be effective in reducing actinic keratosis and BCCs in immune-competent human populations [45]. We and others have shown that ornithine decarboxylase is an important molecular target for the chemoprevention of BCCs and SCCs in experimental animals [46,47]. Carbone et al [48] conducted a Phase 1 trial in 18 OTRs randomized to 0.5 or 1.0 grams of DFMO or placebo in a study designed to investigate the short term toxicity of this agent over a period of 28 days. In this trial they also investigated the effects of DFMO on skin polyamine levels and TPA-induced ODC activity. These experiments suggested that DFMO might be an effective chemopreventive agent in skin cancer. Although a Phase 2b clinical trial of DFMO in OTRs is listed in the Clinical Trials Registry, the results of this trial have not yet been published.

In another study, capecitabine, which is a pro-drug for 5-fluorouracil (5-FU), was tested at low doses as a chemopreventive agent in solid transplant recipients. In this study, the cumulative incidence of SCCs, BCCs and actinic keratoses was significantly reduced with manageable toxicity [49].

There has been considerable support for the use of the m-TOR inhibitor sirolimus based on reports of its ability to reduce skin cancer risk in OTRs. These results were initially based on analysis of retrospective studies indicating that changing the immunosuppressive regimen to a sirolimus-based regimen may reduce the incidence of NMSC. In an assessor-blinded prospective, randomized, controlled trial, switching to sirolimus treatment in renal transplant recipients was assessed for its ability to block NMSCs [50]. This trial demonstrated the superiority of sirolimus therapy in terms of inhibiting the progression of skin cancers as well as promoting the regression of pre-existing premalignant lesions. This study also showed that rapamycin treatment delayed development of premalignancies and reduced the incidence of new NMSCs. Another proliferation signal inhibitor and an analog of sirolimus, everolimus was also found to be a potent anti-neoplastic and immunosuppressive agent [51].

Despite being highly attractive as cancer chemopreventive agents, chronic use of m-TOR inhibitors is associated with a number of side effects which often require discontinuation of the treatment. Among these, dyslipidemia is a common manifestation in these patients and requires treatment with lipid lowering agents. It is believed that m-TOR inhibitors reduce catabolism of apo B₁₀₀ which leads to increased triglycerides and cholesterol in both experimental animals and humans. In addition, decreased lipoprotein lipase activity and increased free fatty acid levels may be contributing factors. Maluf et al [52] suggested that a polymorphism in apo E may influence the degree of hyperlipidemia in kidney transplant patients receiving sirolimus treatment.

In an immune competent population, specific COX-2 inhibitors proved effective in reducing skin cancer risk [53]. However, the use of these agents in OTRs has potential risks particularly in terms of their negative effect on kidney graft and cardiovascular functions. This is based on the fact that the COX-2 inhibitor, celecoxib, was found to be associated with an increase in serious cardiovascular events in individuals at high risk for cardiovascular disease. However, it is conceivable that topical preparations of COX-2 inhibitors or non-specific COX inhibitors may be relatively risk free.

Conclusion

OTRs are at a high risk of skin cancer development. In this population, skin cancer is a source of high morbidity and significant mortality. In addition to various factors that are associated with increased risk of skin cancer in an immune competent population, the skin cancer risk of OTRs is dependent on factors related to the transplanted graft and to treatment protocols. The risk of cancer development increases exponentially with increasing time post transplant. Due to the lack of certainty about the deleterious effects of chemical agents on transplanted organs, the use of chemopreventive agents as an approach to managing skin cancer development has not progressed. The hope for the preventive management of skin neoplasms lies with the observations that certain types of immunosuppressants, particularly those which are mTOR inhibitors, manifest tumor growth blocking effects. Although some of these agents are not well tolerated by OTRs, their use is common in combination with other anti-graft rejection medications. Development of better TOR inhibitors holds promise for skin cancer chemoprevention. In addition, topical agents that proved effective in immune-competent populations should also be tested in OTRs.

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Table 1

Solid Organ Transplant Patients in the United States in 2008

Serial Number	Graft Organ	Number of Cases
1	Total	27,961
2	Kidney	16,517
3	Pancreas after kidney	214
4	Pancreas alone	223
5	Kidney after pancreas	836
6	Intestine	185
7	Liver	6318
8	Heart	2163
9	Heart and Lung	27
10	Lung	1478

Figures taken from OPTN/SRTR data as of May 4, 2009