Skin Cancer after Renal Transplantation

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Abstract

Nonmelanoma skin cancer is the most common cancer in kidney transplant recipients. The most common nonmelanoma skin cancer is squamous cell cancer, with an incidence of approximately 4% per annum in Northern Europe compared to 30% per year in high ultraviolet exposure areas such as Queensland, Australia. Age at transplantation, duration of immunosuppression, previous ultraviolet exposure, and previous nonmelanoma skin cancer are the key factors defining the risk of developing squamous cell cancer in kidney transplant recipients. Irrespective of geography, there appears to be a small minority of kidney transplant recipients who accrue multiple squamous cell cancers, with concomitant morbidity and mortality of approximately 1% per year. This review focuses on the current evidence available to risk-stratify kidney transplant recipients with regards to squamous cell cancer development, risk of metastasis, and death. In particular we focus on the concept of high-risk squamous cell cancer and tumor thickness as the main determinants of squamous cell cancer metastasis risk. Potential strategies to reduce the incidence of high-risk squamous cell cancer, including immunosuppression dose reduction, conversion to mammalian target of rapamycin inhibitor, and enumeration of regulatory T-cells in peripheral blood of kidney transplant recipients, are discussed. This latter technique may also define those kidney transplant recipients who derive benefit from mammalian target of rapamycin inhibitor conversion, i.e. tailored immunosuppression. It is proposed that the management of high-risk squamous cell cancer in kidney transplant recipients be directed by a multidisciplinary team involving the nephrologist, dermatologist, plastic surgeon, histopathologist, and radiation oncologist. (Trends in Transplant. 2013;7:23-30)

Key words


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Introduction

Kidney transplant recipients (KTR) are three-to-five times more likely to develop cancer than the general population and for advanced-stage malignancy have a substantially poorer prognosis\(^1,2\). For nonmelanoma skin cancer (NMSC) and in particular the most prevalent type of NMSC, cutaneous squamous cell carcinoma (SCC), the increased risk can be 60-250-fold\(^3,5\). It is expected that half of all white organ transplant recipients will experience NMSC at some point after organ transplantation\(^6\). In addition, KTR who develop SCC are at an increased risk of developing non-cutaneous cancer\(^7,8\).

Factors associated with squamous cell carcinoma development post renal transplantation

Prospective cohort studies of KTR in Northern Europe have defined SCC incidence at around 3.5% per annum\(^9\). However, the incidence is substantially higher in high ultraviolet (UV) light exposure environments, such as subtropical Queensland, Australia, where the overall incidence approaches 30% per annum\(^10\). In addition, whereas KTR in Northern Europe tend to accrue singular tumors per year, those in subtropical Queensland accrue multiple tumors per year\(^10\).

The development of SCC is related to time after transplant. In a prospective study in the UK, 4/230 (1.8%) KTR developed SCC within five years of transplantation. With longer-term follow-up > 10 years, 34/230 (14%) developed at least one SCC, 18/34 (53%) developed more than two SCC, and 5/34 (15%) developed more than five SCC. These figures are similar to other European studies, with 88% of KTR developing multiple SCC within the five-year period following their first SCC\(^11,12\). It is believed that the time to next SCC after the first SCC is approximately 15 months, and 12 months to develop a third SCC\(^13,15\). However, in recent controlled trials from Northern Europe and the UK for secondary prevention of SCC in KTR, time to second and subsequent SCC was > 18 and > 24 months, respectively\(^16,17\). This may also reflect baseline UV exposure as a similar randomized controlled trial in Australia had a median time to next tumor of nine months\(^18\).

On an individual level, the clinical parameters associated with increased risk of SCC posttransplant include: intensity and duration of previous UV exposure; recalled history of blistering sunburn; and age at transplant and previous history of sun damaged skin and NMSC\(^5,10,19\). At the time of transplant assessment, it is possible to have an evidenced-based approach to predict time to first SCC and therefore advise on the necessary dermatological review periodicity\(^20\). In fact, after transplantation it is also possible to use similar evidenced-based clinical indices to predict the number of SCC accrued over the next 12 months\(^10,21\).

Metastatic squamous cell skin carcinoma and outcome in kidney transplant recipients

Irrespective of time to develop multiple SCC, there is still a small but significant cohort of KTR who accrue multiple SCC, which are associated with significant morbidity. Up to 3% of KTR populations per year undergo extensive plastic surgical procedures requiring in-patient stays in hospital\(^9,10\). The KTR populations have an incident mortality of 1-4% for metastatic SCC\(^10\), which is related to the dose of immunosuppression, with heart transplant recipients having the highest SCC-related mortality rates and immunosuppression doses\(^22\).

In prospective studies, in a large cohort of predominantly non-immunosuppressed
subjects, the most significant clinicopathologic parameter predicting SCC metastasis was tumor thickness with almost no risk of spread < 2.8 mm\(^2\). Risk of spread was 4% in tumors 2-6 mm, and 16% in those thicker than 6 mm. However, the risk of spread for any stage or grade was three-times higher for patients taking immunosuppression. The aggressiveness of SCC in KTR is reflected in the one-year mortality rate from metastatic SCC in organ transplant recipients, which approaches 60%\(^2\), whereas two-year mortality is only 20% in the general population with metastatic SCC\(^2\). This attrition is also reflected in data from the ANZDATA registry shown in figure 1.

The clinical impact of SCC or solid organ cancer on KTR populations is illustrated by registry data showing death from any cancer is in some countries (Australia) becoming the leading cause of death of KTR who have a functioning graft. Death from SCC is one of the largest contributors to cancer death\(^2\).

The primary reason for this clinical predicament is that not only do immunosuppressive drugs suppress immune responses to the allograft, but they may also impair antitumor responses\(^2\). Immunosuppressive agents can have indirect mutagenic effect, leading to the elaboration of the mediators that are pro-carcinogenic\(^2\). These issues will be discussed in the following sections.

**Immunosuppressive regimen and squamous cell carcinoma risk**

Whereas immunosuppressive exposure leads to a greater risk of SCC\(^3\), there are conflicting data regarding the impact of the calcineurin inhibitors (CNI), tacrolimus and cyclosporine, mycophenolate acid, and azathioprine on SCC risk in the context of solid organ transplantation\(^3\). The only immunosuppressants consistently associated with reduced de novo cancer risk are the mammalian target of rapamycin inhibitors (mTORi)\(^3\).

Before it was used in transplantation, azathioprine was associated with malignancy after prolonged treatment of autoimmune disorders\(^3\). Azathioprine is thought to increase SCC risk due to its incorporation into DNA.
This incorporation causes DNA to absorb more UV energy and creates reactive oxygen species, which are directly mutagenic\textsuperscript{39,40}. However, when compared to CNI-based regimens, azathioprine and prednisolone regimens have been associated with fewer skin malignancies\textsuperscript{41}.

Both cyclosporine and tacrolimus have been shown to promote progression of cancer in mice by increasing synthesis of transforming growth factor beta (TGF-\(\beta\)), interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) in tumor cells, thereby enhancing tumor growth, metastasis, and angiogenesis\textsuperscript{29,31,42}. From a preventative perspective, there is only one prospective randomized controlled trial suggesting reduced CNI dose results in fewer cancers developing\textsuperscript{34}. In this study, 231 KTR were randomized to low or standard dose cyclosporine. After a follow-up of 66 months, there were 26 NMSC, predominately SCC, in the standard cyclosporine dose group and 17 NMSC in the reduced dose group (\(p < 0.05\)).

Steroids act primarily by blocking the nuclear factor kappa-B pathway, which can lead to skin malignancy\textsuperscript{43,44}. In non-KTR taking oral corticosteroids, there is an increase risk of SCC\textsuperscript{45} and Kaposi’s sarcoma\textsuperscript{46}. In case-control studies, steroid usage has been associated with SCC development in long-term immunosuppressed KTR\textsuperscript{47}. Meta-analysis of steroid-free regimens in KTR has shown reduced incidence of cancer after five years, but these observations did not reach statistical significance\textsuperscript{48}.

The inhibitors of the intracellular mammalian target of rapamycin (mTOR) pathway, sirolimus and everolimus, inhibit the intracellular effects of VEGF, reduce levels of TGF-\(\beta\), and sensitize tumor cells to apoptosis\textsuperscript{49}. There is strong evidence \textit{in vitro} and in animal models that mTORi inhibit malignant transformation. There are three randomized controlled trials involving sirolimus for secondary prevention of SCC in KTR, and these are summarized in table 1 and reviewed elsewhere\textsuperscript{50}. Although, in a population-based approached, new SCC was reduced by 40% on conversion to mTORi, there were major issues with tolerability so that only 30-50% of KTR were able to tolerate mTORi in the long term\textsuperscript{16-18}. However, in those KTR who tolerated mTORi, the reductions in new SCC approached 60%.

In subgroup analysis, there was also a suggestion that mTORi are not beneficial for secondary prevention of SCC in KTR with more than two SCC\textsuperscript{16,17}. This leads to questions as to how to manage KTR with aggressive SCC who do not tolerate mTORi or continue to accrue high-risk lesions whilst on therapy.

Unfortunately, there are only limited case series data showing that immunosuppressive dose reduction after SCC reduces the chance of death from metastatic SCC, the likelihood of metastasis, or subsequent SCC development\textsuperscript{51,52}. Around two-thirds of KTR will develop fewer SCC after reduction or cessation of immunosuppression, and therefore the converse is also true; that after drug cessation one-third of KTR can still accrue SCC.

For those who have failed to derive benefit from the aforementioned options, there is evidence that adding low-dose capecitabine to preexisting immunosuppressive regimens is efficacious\textsuperscript{53}. In this study of 15 solid organ transplant patients, new SCC development fell to a third of pretreatment levels, with a discontinuation rate of 33% at one year.

In our local experience (\(n = 4\)) we have found that cessation of antiproliferative and partial reduction in prednisolone and sirolimus and the addition of capecitabine has been efficacious in reducing the number of new SCC and the severity of the histological
One patient was unable to tolerate capecitabine. There have been no deteriorations in graft function with this alteration in the drug regimen.

**Future options**

As in the general population, UV exposure increases the risk of SCC in KTR. Ultraviolet light is directly mutagenic to DNA, in particular inducing p53 mutations. The p53 is a tumor suppressor gene, it is responsible for inducing apoptosis in cells with irretrievably damaged DNA, and is the prime mechanism preventing epidermal carcinogenesis. Around 90% of SCC have this mutation and are therefore resistant to apoptosis.

Importantly, UV light is also immunosuppressive and induces keratinocytes to secrete IL-10, which in turn prevents Langerhans cells from activating T-cells. Post UV exposure to the skin, Langerhans cells in the epidermis migrate to local lymph nodes and undergo apoptosis. The migrating Langerhans cells contain pyrimidine dimers, specific to UV-induced damage, and are functionally impaired, with reduced major histocompatibility complex class II, intercellular adhesion molecule-1, and B7 expression. These UV-induced antigen-presenting cells are involved in the suppression of cutaneous immunity and can generate regulatory T-cells (T\(_{\text{reg}}\))

This interaction of cell-mediated immunity of T\(_{\text{reg}}\) cells has been found to predict...
aggressive behavior of cancer in the general population. Indeed, the predominance of T\textsubscript{reg} cells in SCC from KTR compared to SCC from non-immunosuppressed subjects has been hypothesized as one of the reasons cancer is more aggressive in KTR.

Indeed, we have also investigated whether T\textsubscript{reg} cells in peripheral blood are a marker of increased SCC risk. In the United Kingdom KTR populations, the number of T\textsubscript{reg} cells in peripheral blood was additive with previous SCC history in predicting those with KTR at risk of developing new SCC. In addition, we have also shown that KTR converted to mTORi who have increased number of T\textsubscript{reg} cells are those KTR who continue to accrue SCC in spite of conversion to mTORi. Therefore, T\textsubscript{reg} testing may predict those who do not derive benefit from conversion to mTORi.

Conclusions

All of these data assume KTR with SCC have regular dermatological follow-up and the recommendations here are for the transplant physician to consider manipulations in immunosuppression in high-risk situations. The transplant physician is reminded to consider post-surgical radiotherapy for any high-risk lesion in their KTR to prevent recurrent of SCC.

In summary, SCC is a major clinical problem for a minority of KTR, and previous SCC is one of the major risk factors for new SCC development. In KTR with high-risk lesions (invading deep reticular dermis or > 2.8 mm thick), the risk of metastasis and death is not insubstantial and some thought to manipulation of immune suppression should be considered.

The mTORi have offered some hope, but they are not always well tolerated and may not be efficacious in those with multiple SCC. Capecitabine offers some hope and “simple” dose reduction in those with high-risk lesions may be safe, though there is always the risk of precipitating rejection.

References


