Use of proliferation signal inhibitors in non-melanoma skin cancer following renal transplantation

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Abstract
Non-melanoma skin cancer (NMSC) affects a large proportion of renal transplant recipients, with estimates suggesting that at least half of white-skinned transplant recipients will develop NMSC following transplantation. Squamous-cell carcinoma is the most frequent NMSC following transplantation occurring at a 100-times greater risk than in the general population, while the incidence of basal cell carcinoma is increased 10-fold over the general population. The most important risk factor for the development of NMSC in renal transplant recipients is prior exposure to ultraviolet radiation, therefore, geographical location and skin type highly influence the risk of NMSC. However, both the intensity and type of immuno-suppressive therapy have been associated with an increased risk of NMSC. Given the potential anti-cancer actions of the proliferation signal inhibitors (PSIs), everolimus and sirolimus, demonstrated in both pre-clinical and clinical studies, we have analysed the effect of conversion to PSIs in 53 renal transplant recipients developing NMSC after transplantation. Remission of NMSC was observed in 37 patients and was generally well tolerated with minimal adverse events reported. Fifteen patients developed new lesions following conversion, two of these were receiving low-dose calcineurin inhibitors (CNIs) as part of their immuno-suppressive regimen suggesting that there was insufficient reduction of CNIs. PSI blood levels did not seem to affect the outcomes of conversion. These data, along with published clinical trial data suggest that conversion from CNIs to PSIs may be useful in the management of NMSC following renal transplantation.

Keywords: non-melanoma skin cancer; post-transplant malignancy; proliferation signal inhibitors/ mammalian target of rapamycin inhibitors; renal transplant recipients

Introduction
Non-melanoma skin cancer (NMSC) is a significant clinical problem in organ transplant recipients, and is likely to increase in importance as patients and graft survival times continue to lengthen. Overall, basal-cell (BCCs) and squamous-cell carcinomas (SCCs) account for >90% of all NMSC occurring in transplant recipients [1]. The tumours are often associated with multiple warts or pre-malignant in situ conditions, such as Bowen’s disease and actinic keratoses. No patient has been reported to die from BCCs and SCCs occurring in transplant recipients, although tumours in these patients are generally more aggressive than those appearing in other populations [2]. Older age, those with multiple extracutaneous or cephalic tumours and high sun exposure also contribute to a worse prognosis [1]. This review discusses the increased risk and pathogenesis of NMSC post-transplantation, specifically highlighting the impact of immuno-suppressive regimens on the incidence of NMSC in renal transplant recipients.

Pathogenesis
Skin carcinomas have a multifactorial pathogenesis, with both intrinsic and extrinsic factors [1]. There are many types of NMSC, with SCCs and BCCs, originating from epidermal and hair-follicle keratinocytes being the most frequent tumours. [1]. Life-long immuno-suppression [with calcineurin inhibitors (CNIs) or anti-metabolites] is the most important risk factor for the development of NMSC. In addition, environmental (UV-exposure, human papilloma virus infections) and genetic factors (fair skin, genetic polymorphisms) are suspected to play a role in the early stages of SCC development, in which certain mutations in tumour suppressor (p53) and proto-oncogenes may occur [1]. Other, less common skin cancers include Kaposi’s sarcoma, originating from endothelial cells; Merkel cell carcinoma, originating from neuroendocrine cells; primary cutaneous lymphomas and sarcomas [1].
Epidemiology

Skin carcinoma is the most common cancer in white populations, with >15000 new cases annually in The Netherlands alone, a number that is still rising [3]. It is estimated that at least half of all white-skinned transplant recipients will develop at least one NMSC after receiving a transplant. Overall, the cumulative incidence of NMSC after transplantation ranges from 2–24% after 5 years to 7–33% after 10 years [4]. SCC in particular is the most common form of skin cancer in transplant recipients, occurring at an incidence 65–250 times greater than in the general population, while the incidence of BCC is increased 10-fold after transplantation [1]. This means that the normal ratio of 4:1 BCC to SCC is reversed in transplant recipients [1,5].

There is considerable evidence to suggest that the most important risk factor for the development of NMSC in immuno-compromised individuals is prior exposure to ultraviolet radiation, which, in addition to its role as a mutagen, also has immunosuppressive properties in the skin [1,4]. The tumours tend to develop on areas of the skin that are regularly exposed to the sun, such as the face and forearms, and the risk of developing a tumour is significantly increased in patients with a high lifetime sun exposure, particularly exposure occurring before the age of 30 years [6,7]. In addition, Caucasian transplant recipients with fair skin and a tendency to sunburn are at a higher risk of NMSC after transplantation than those with darker skin that tans on sun exposure [7]. Evidence of the role for ultraviolet light comes from the increased incidence of NMSC in fair-skinned populations living in countries with a hot climate and high ultraviolet exposure compared with those living in more temperate regions. For example, the 10-year incidence of NMSC in renal transplant recipients varies from 7% in Norway to 9–10% in Italy and UK, and ≥33% in Australia [4]. Indeed, the highest global risk of post-transplant NMSC occurs in Caucasian patients living in the northern states of Australia [8]. When the incidence of post-transplant NMSC in Queensland was compared with that in The Netherlands, patients in the Australian cohort were around four times more likely to develop NMSC, even after adjustment for sex and age at first transplantation (Figure 1) [9].

Fig. 1. Cumulative incidence (±95% confidence intervals) of skin cancer in patients from Australia and The Netherlands [8] (Reprinted with permission from Lippincott, Williams and Wilkins). BCC NL, basal-cell carcinoma in The Netherlands; SCC QU, basal-cell carcinoma in Queensland; CA NL, all skin cancer in The Netherlands; CA QU, all skin cancer in Queensland; SCC NL, squamous cell carcinoma in The Netherlands; SCC QU, squamous cell carcinoma in Queensland.

The adjusted relative risk was greater for BCC (5.1) than for SCC (3.6). In addition to sun exposure, a number of other risk factors for post-transplant NMSC have been identified. A UK study in renal transplant recipients found that older age at transplantation, presence of premalignant lesions such as actinic keratoses, and male sex were associated with the development of BCC and SCC, while a history of cigarette smoking was also associated with development of SCC [5]. A study of heart transplant recipients in Spain, however, found that total sun burden and skin type were the only significant risk factors after multivariate analysis, with age at transplantation significant only in the crude analysis, and no relationship detected between NMSC and sex, incident warts or history of smoking [7].

Immunosuppressive regimens and NMSC

As with all post-transplant malignancies, immunosuppression is a critical component of the increased risk, although the contribution of individual agents is less clear. A study carried out in Queensland showed no difference in the risk of developing skin cancer between patients receiving ciclosporin (CsA) or azathioprine and those receiving combination therapy with both agents [9]. Support for the role of the total level of immuno-suppression in the development of NMSC came from a study by Dantal et al. [10], in which patients were randomized to normal- or low-dose CsA therapy (trough blood levels of 150–250 ng/ml and 75–125 ng/ml, respectively). The results showed that both the overall risk of cancer and the risk of skin cancers were significantly decreased in the low-dose CsA group (P < 0.05) (Table 1). The low-dose regimen was, however, associated with a significant increase in the risk of acute rejection. Studies of newer immuno-suppressive agents are limited, although a study in renal transplant recipients showed that tacrolimus was associated with a significantly lower incidence of NMSC compared with CsA [11]. A study in liver transplant recipients showed that mycophenolate mofetil (MMF) was associated with an increased risk of NMSC, although this risk did not remain after multivariate analysis [12].
Non-melanoma skin cancer: the role of PSIs following renal transplantation

In addition to the level of immunosuppression, the duration of immuno suppression also appears to play a role in the development of NMSC. A study carried out in Queensland showed that the cumulative incidence of skin cancer increased progressively, from 7% after 1 year of immunosuppression to 45% after 11 years and 70% after 20 years [9]. A more recent study in a similar population showed that the overall incidence of NMSC increased from 19% at fewer than 5 years to 47% after more than 20 years of immuno-suppressive therapy [13].

Conversion to proliferation signal inhibitors (PSIs)

Following on from promising experimental models demonstrating the anti-neoplastic potential of sirolimus, the rates of malignancy at 2 years after renal transplantation were reviewed in patients receiving sirolimus therapy in combination with CsA, sirolimus as base therapy or sirolimus maintenance therapy after early withdrawal of CsA. At 2 years post-transplant, patients receiving a combination of sirolimus and CsA had a lower incidence of NMSC compared with patients who received placebo. The incidence of malignancy was significantly lower in patients receiving sirolimus with early CsA elimination than in patients who remained on sirolimus and CsA therapy [14]. Compared with a 5% incidence in CsA-treated patients, no malignancies were observed in patients receiving sirolimus as base therapy [14]. The potential anti-tumour benefits of CsA elimination from a sirolimus-based therapy were further examined in a post hoc analysis of 430 renal transplant recipients [15] randomly assigned at 3 months post-transplantation to remain on sirolimus, CsA and steroids or to have CsA withdrawn from the regimen and sirolimus trough levels increased by twofold. At 5-year follow-up, the median time to a first skin carcinoma was longer and the mean annualized rate was significantly lower in the sirolimus group than in the CsA/sirolimus group [15]. The relative risks for both BCC and SCC were significantly reduced, indicating that a CsA-free, sirolimus-based immuno-suppressive regimen may reduce the incidence of post-transplant skin malignancies.

To gain a better understanding of current clinical experience of conversion to a PSI in patients with NMSC, patient data from eight transplant centres across Europe were pooled. This analysis only included renal transplant recipients who were converted to PSIs following the development of NMSC. In total, 53 renal transplant recipients who developed NMSC were converted to PSIs, of these, eight patients received everolimus and 45 patients received sirolimus; CNIs were withdrawn in 51 patients and minimized in two patients (Table 2). Sirolimus blood levels ranged from 5 to 11 ng/ml and everolimus blood levels ranged from 2 to 8 ng/ml. Remission of NMSC occurred in 37 patients and was generally well tolerated; reported adverse events included acniform skin eruptions (n = 9), aphthous ulceration (n = 2), pneumonitis (n = 1), anaemia (n = 1), oedema (n = 3) and proteinuria (n = 2). Relapse of cancer occurred in 15 patients, of those, two patients were receiving a CNI-minimization protocol although for the remaining patients the analysis suggests that a relapse of cancer is not related to PSI blood levels. One patient was lost to follow-up, one patient with previously advanced chronic allograft nephropathy returned to dialysis and five died. These data suggest that whilst PSIs might aid the management of NMSC, patient history is also likely to influence the outcome following conversion.

Summary

The incidence of NMSC is higher in patients receiving kidney transplants compared with those in the general population. Although BCCs and SCCs are not usually life-threatening, they have an impact on patient quality of life and require treatment. Although standard surgical treatments for skin cancer are usually effective, reducing the risk for multiple new primary skin cancers remains a challenging problem. The potential for PSIs in reducing the impact of NMSC following renal transplantation has been observed in a number of clinical studies, and increasing clinical experience with this regimen may provide further insights into

### Table 1. Frequency of skin cancers in patients receiving low- or normal-dose ciclosporin [10]

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<tr>
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<th>Normal-dose CsA*</th>
<th>Low-dose CsA*</th>
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<tr>
<td>Squamous-cell carcinoma</td>
<td>13%</td>
<td>7%</td>
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<tr>
<td>Bowen’s disease</td>
<td>2%</td>
<td>4%</td>
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<tr>
<td>Basal-cell carcinoma</td>
<td>8%</td>
<td>3%</td>
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<tr>
<td>All skin cancers</td>
<td>23%</td>
<td>15%</td>
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*CsA, ciclosporin.

### Table 2. Clinical experience of PSIs in non-melanoma skin cancer from eight European Transplant centres

<table>
<thead>
<tr>
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<th>Recurrent NMSC* (n = 15)</th>
<th>NMSC^a-free (n = 37)</th>
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<tbody>
<tr>
<td>Age at follow-up (mean and range)</td>
<td>66 (54–82) years</td>
<td>69 (47–79) years</td>
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<tr>
<td>First NMSC post-transplant (mean ± SD)</td>
<td>4.1 ± 4.2 years</td>
<td>7.2 ± 5.5 years</td>
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<tr>
<td>Number of NMSCs before conversion (mean and range)</td>
<td>4 (1–25)</td>
<td>2 (1–18)</td>
</tr>
<tr>
<td>Conversion after first NMSC (mean ± SD)</td>
<td>4.0 ± 3.3 years</td>
<td>4.0 ± 4.6 years</td>
</tr>
<tr>
<td>NMSC-free on PSI (mean and range)</td>
<td>10 (3–23) months</td>
<td>24 (2–51) months</td>
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*NMSC, non-melanoma skin cancer; PSI, proliferation signal inhibitor.
management of the disease. At present several multi-centre studies are underway that should provide evidence-based guidance on the role of PSI's in the management of NMSC.

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References