Use of proliferation signal inhibitors in the management of post-transplant malignancies—clinical guidance

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Abstract

Increasing success in renal transplantation and longer patient survival has meant that post-transplant malignancies are having an increasing impact on long-term graft and patient survival. Choice of the immunosuppressive agents provides one of the controllable risk factors for the development of malignancies in this population. Calcineurin inhibitors (CNIs) are associated with an increased incidence of cancers, whereas the proliferation signal inhibitors (PSIs), everolimus and sirolimus have demonstrated anti-oncogenic effects in pre-clinical models and are currently being investigated as anti-cancer agents in clinical trials. There is increasing evidence demonstrating a lower incidence of post-transplant malignancies in renal transplant recipients receiving PSI-based immunosuppression compared with those receiving CNIs. Conversion from CNIs to PSIs has been shown to lead to the regression of Kaposi’s sarcoma in renal transplant recipients and is now part of accepted standard care for this tumour in this setting. The anti-cancer properties of PSI-based regimens have the potential to combine the dual benefits of immunosuppression without the use of CNIs and the direct anti-oncogenic effects through their inhibition of the mammalian target of rapamycin (mTOR) signalling pathway. In the absence of formal clinical trial evidence on the best way to use PSIs in this setting, a workshop was held to provide practical guidance on immunosuppressive strategies in the context of malignancy, given the current state of knowledge.

Keywords: immunosuppression; malignancy; proliferation signal inhibitors/mTOR inhibitors; renal transplant

Introduction

Transplant patients are surviving longer now than they did 10 years ago and, as they do so, malignancies become an increasing burden [1,2]. Compared with the general population, renal transplant recipients have an overall 3–5-fold higher risk of malignancy [3,4]. The most commonly observed malignancies in renal transplant recipients include non-melanoma skin cancers and post-transplant lymphoproliferative disorders (PTLD), with an overall 3–5-fold higher risk of malignancy [3,4]. The most commonly observed malignancies in renal transplant recipients include non-melanoma skin cancers and post-transplant lymphoproliferative disorders (PTLD), with a 10–30-fold increase compared with the general population, and kidney cancer, with approximately a 10-fold increase [5]. Kaposi’s sarcoma also occurs more frequently than in non-immunosuppressed individuals and is a common...
tumour in some transplant populations, but rare in others. There is also a higher risk of some solid organ tumours such as colon, lung, bladder and larynx cancer, with a 2–5-fold increase [5].

Both the duration and intensity of immunosuppression have been linked to the increased incidence of malignancies reported in transplant recipients [6–8]. However, the incidence of post-transplant malignancies following renal transplantation may in part be attributed to the choice of immunosuppressive therapy. Furthermore, there are a number of reports which suggest that different immunosuppressive agents may be associated with different levels of risk (Table 1); these have been reviewed in accompanying papers and other recent publications [9–12]. The proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) and sirolimus (Rapamune®, Wyeth Pharmaceuticals, USA) have anti-proliferative and anti-angiogenic actions, leading to specific inhibition of tumour growth in pre-clinical models [13–16]. This is as a result of their ability to inhibit cellular signalling pathways involved in critical functions such as cell division, T-cell activation, invasion and growth factor production. PSIs form a complex which inhibits signalling via mTOR, a key molecule of the phosphatidylinositol-3-kinase (PI3K) pathway, which is constitutively activated in many tumours [17,18].

Clinical studies in renal transplant recipients support the initial data and report lower malignancy rates in PSI-treated patients compared with those receiving CNIs [19–21]. The lower rate of malignancies in these studies may be explained either by the direct anti-oncogenic effects of this class of drugs or by the minimization or elimination of CNIs that they enable [22–24]. Sirolimus is used in CNI-free strategies, and everolimus is currently being investigated in this setting. Pending formal clinical trial data, clinicians are exploring options for patients with established malignancies after transplantation, driven by the evidence to date. A workshop focused on the current clinical data was held to debate the practical clinical options available. This article summarizes the discussions and attempts to provide practical guidance on

Table 1. Impact of immunosuppressive agents on the risk of post-transplant malignancies

<table>
<thead>
<tr>
<th>Immunosuppressive therapy</th>
<th>Organ</th>
<th>Observations/results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OKT3/ATG induction therapy</td>
<td>Heart/kidney/other</td>
<td>Increased risk of lymphoma</td>
<td>[48]</td>
</tr>
<tr>
<td>IL-2 induction therapy</td>
<td>Heart/kidney/other</td>
<td>No increased of lymphoma</td>
<td>[48]</td>
</tr>
<tr>
<td>OKT3/ATG</td>
<td>Kidney</td>
<td>Increased risk of lymphoma</td>
<td>[49]</td>
</tr>
<tr>
<td>Anti-metabolites</td>
<td></td>
<td></td>
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<tr>
<td>Azathioprine</td>
<td>Kidney</td>
<td>Reduced risk of lymphoma</td>
<td>[49]</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>Kidney</td>
<td>No increased risk of lymphoma</td>
<td>[50]</td>
</tr>
<tr>
<td>MMF</td>
<td>Kidney</td>
<td>Reduced risk of lymphoma or other malignancies in UNOS or CTS registries</td>
<td>[49]</td>
</tr>
<tr>
<td>MMF vs azathioprine</td>
<td>Kidney</td>
<td>Decreased risk of PTLD with MMF</td>
<td>[51]</td>
</tr>
<tr>
<td>MMF vs No MMF</td>
<td>Kidney</td>
<td>Increased risk of in Kaposis’s sarcoma, possibly due to MMF</td>
<td>[52]</td>
</tr>
<tr>
<td>CNIs</td>
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<tr>
<td>Tacrolimus vs new CsA</td>
<td>Kidney</td>
<td>higher risk of lymphoma with tacrolimus</td>
<td>[49]</td>
</tr>
<tr>
<td>formulations (no induction therapy)</td>
<td></td>
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<td></td>
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<tr>
<td>Tacrolimus vs CsA</td>
<td>Liver</td>
<td>No difference in rate of neoplastic disease</td>
<td>[53]</td>
</tr>
<tr>
<td>Tacrolimus vs CsA</td>
<td>Heart/kidney/other</td>
<td>Doubled risk of lymphoma with tacrolimus</td>
<td>[48]</td>
</tr>
<tr>
<td>CsA</td>
<td>Kidney</td>
<td>Three-fold increase in non-melanoma skin cancer</td>
<td>[54]</td>
</tr>
<tr>
<td>CsA in maintenance therapy</td>
<td>Heart/kidney/other</td>
<td>Increased risk of neoplastic disease</td>
<td>[55]</td>
</tr>
<tr>
<td>Full-dose CsA vs low-dose CsA</td>
<td>Kidney</td>
<td>No increased risk of lymphoma</td>
<td>[48]</td>
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<tr>
<td>CNI vs antimetabolites</td>
<td>Kidney</td>
<td>Dose-dependent increase in cancers</td>
<td>[6]</td>
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<tr>
<td>CsA vs azathioprine</td>
<td>Kidney</td>
<td>Increased risk of cutaneous dysplasia with CsA</td>
<td>[56]</td>
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<tr>
<td>PSI vs CNI</td>
<td>Kidney</td>
<td>Increased risk of all cancer and skin cancers with CsA</td>
<td>[21]</td>
</tr>
<tr>
<td>Sirolimus + CsA vs sirolimus and no CsA</td>
<td>Kidney</td>
<td>Increased risk of all cancers with CsA</td>
<td>[20]</td>
</tr>
<tr>
<td>Sirolimus vs CsA</td>
<td>Kidney</td>
<td>Increased risk of all cancers with CsA</td>
<td>[19]</td>
</tr>
</tbody>
</table>

ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; CsA, ciclosporin; CTS, Collaborative Transplant Study; IL, interleukin; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor; PTLD, post-transplant lymphoproliferative disorder; UNOS, United Network for Organ Sharing.
immunosuppressive strategies for the use of PSIs in malignancies.

**Clinical guidance: PSIs in renal transplant recipients with a pre-existing history of malignancy**

There are a number of published reports supporting the observation that renal transplant recipients with a history of malignancy are at a high risk of recurrence following the introduction of immunosuppressive therapies. Patients with a history of multiple skin cancers prior to transplant have been reported to be at very high risk of multiple skin cancers [25]. In agreement with the outcomes of several randomized, controlled trials demonstrating a lower incidence of de novo malignancy or non-skin solid tumours in renal transplant recipients receiving PSIs after early withdrawal of CNIs [19,21], and based on pre-clinical data [26], it is possible that PSI-based immunosuppression could be considered in patients with a pre-existing, or history of, malignancy. It may be possible to identify other patients at higher than average risk of developing post-transplant malignancy for whom a pre-emptive or early conversion strategy may also be warranted. Such an early conversion strategy rather than a pre-emptive approach may help to ensure that adequate immunosuppression is achieved early post-transplant. Furthermore, the use of PSIs early post-transplant may help to reduce the exclusion time on wait-list for patients with a history of malignancy.

**Clinical guidance: PSIs in renal transplant recipients who develop post-transplant malignancies**

Pilot studies and published experience from several centres demonstrate that PSIs may be beneficial for the treatment of Kaposi’s sarcoma, recurrent skin cancer, renal cell carcinoma and some solid tumours (Table 2).

Conversion from CNIs to PSIs has been shown to cause regression of Kaposi’s sarcoma [27–29] and registry and clinical study data show that PSI treatment has been associated with a lower incidence of skin cancer [21] and non-skin solid malignancy [19]. Furthermore, data from clinical oncology studies indicate that PSIs show promise in the treatment of advanced or metastatic renal cell carcinoma [30,31].

The potential of PSIs in renal transplant recipients with PTLD is not clear, with very limited published clinical evidence for a beneficial role of these agents [32,33]. Treatment of PTLD requires reduction of immunosuppression [34] and it is increasingly common to use rituximab as first-line therapy [35–37], followed by chemotherapy using cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) when there is recurrence [38,39]. The strategy of combined rituximab and conversion from CNIs to PSI has been reported to be successful in a small number of cases [40] and requires investigation in clinical trials to determine its effects.

Solid organ cancers in renal transplant recipients are often more aggressive and have a worse prognosis than those in the general population, and life expectancy in these patients is low [41]. In patients with disseminated disease and a poor prognosis, changes to the immunosuppressive regimen may provide little benefit to the patient’s quality of life and jeopardize remaining renal function. There is more potential gain from targeting patients with a reasonable prognosis aimed at slowing progression of tumour growth and prolonging life expectancy [42].

Conversion to PSIs in liver transplant recipients with hepatocellular carcinoma has, for example, led to regression of metastases at distant sites, including the lungs and ovaries [43,44].

**Table 2. Types of malignancy which may benefit from proliferation signal inhibitors**

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Evidence of impact</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Post-transplantation pilot studies</td>
<td>[27–29]</td>
<td>Rapid resolution of lesions through a VEGF-suppression mechanism</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Clinical trial data</td>
<td>[20,21]</td>
<td>Long-term control uncertain</td>
</tr>
<tr>
<td>Renal cell</td>
<td>Small centre studies</td>
<td>[57]</td>
<td>Conversion to PSI with CNI elimination associated with reduced incidence of skin cancers</td>
</tr>
<tr>
<td>carcinoma</td>
<td>Oncology clinical trial data</td>
<td>[30,31]</td>
<td>Conversion from CNI to PSIs leads to good evolution of skin cancer</td>
</tr>
<tr>
<td>PTLD</td>
<td>Case studies</td>
<td>[40]</td>
<td>Partial response of renal cell carcinoma to PSI treatment</td>
</tr>
<tr>
<td>Solid organ</td>
<td>Registry data</td>
<td>[19]</td>
<td>PTLD successfully treated with rituximab and conversion to PSIs</td>
</tr>
<tr>
<td>tumours</td>
<td>Case studies from liver transplantation</td>
<td>[43,44]</td>
<td>Reduced incidence of non-skin cancers associated with PSIs and CNI elimination</td>
</tr>
<tr>
<td></td>
<td>Oncology clinical trial data</td>
<td>[45]</td>
<td>Treatment of hepatocellular carcinoma and metastases</td>
</tr>
</tbody>
</table>

CNI, calcineurin inhibitor; PSI, proliferation signal inhibitor; PTLD, post-transplant lymphoproliferative disorder; VEGF, vascular endothelial growth factor.

**How should PSIs be used in post-transplant malignancies?**

The use of PSIs in patients with cancer after renal transplantation has two separate approaches, which
may require different dosing strategies. The first of these is the use of PSIs with therapeutic intent directly used to treat a cancer. Ongoing phase I and Phase II clinical trials in oncology are currently using high doses of PSIs, with everolimus doses of 5 mg/day or 10 mg/day currently under investigation [30,45]. Phase III trials are ongoing. These doses are much higher than those recommended in renal transplantation, where doses of 1.5 mg/day or 3.0 mg/day are routinely used to obtain everolimus trough blood levels of 3–8 ng/ml [23,46]. Such doses will be associated with a higher incidence of PSI-related adverse events, including skin disorders, hyperlipidaemia and anaemia [23]. Although higher drug levels may be potentially active and accepted in individual patients with Kaposi’s sarcoma uncontrolled on conventional dosing, there are currently no definitive data to support this approach with other post-transplant malignancies.

The alternative approach is to use the introduction of a PSI to reduce or eliminate CNI-based immunosuppression [22–24]. Where PSIs are used in this setting, it seems reasonable to target lower PSI doses and blood levels sufficient to prevent graft rejection.

**Treatment strategies for PSIs**

There are no evidence-based guidelines for the use of PSIs in renal transplant recipients with malignancies. Most cancer after transplantation has such a poor prognosis that it is recommended to consider all current published clinical experience before advising on treatment strategies. In the absence of trial-driven data, it is important to recognize that treatment must be individualized for the specific circumstances of each patient.

As mentioned previously, conversion from CNIs to PSIs has been associated with regression of Kaposi’s sarcoma [27–29] and solid tumour metastases [43,44]. This approach is then supported in renal transplant recipients who develop post-transplant Kaposi’s sarcoma and recurrent squamous skin cancer. Emerging data from clinical oncology trials suggest that conversion to PSIs could be recommended in patients with post-transplant renal cell carcinoma [30,31]. From clinical experience, it is recommended that PSIs should be introduced rapidly in these patients, with doses and blood levels determined by the type and stage of malignancy and the transplant situation (Figure 1). However, if surgical approaches are also needed, potential wound healing complications in some cases mandate a brief delay until the wound has healed [47]. Once PSI blood levels are achieved, CNIs should be tapered rapidly. In addition, azathioprine or mycophenolic acid-based immunosuppressants could also be tapered over a 1-week to 3-month period, while steroids should be maintained (Figure 1).

**Conclusions**

Pre-clinical and clinical studies provide reasonable evidence for the potential of PSIs in the management of post-transplant malignancies, an effect based both on direct anti-oncogenic activity, particularly
with Kaposi’s sarcoma and indirectly through the minimization or elimination of CNIs. Individual treatment strategies will continue to be used in the management of these clinical problems, driven by the high mortality rates associated with conventional approaches. Transplant recipients with aggressive malignancies should be offered the best and most feasible oncology treatment in addition to the choice of immunosuppressive therapy. Clinical experience of both everolimus and sirolimus in transplant recipients in the absence of current clinical trial data provides support for conversion from CNIs to PSIs in these circumstances. Although PSIs cannot be considered as primary therapy for cancers, and should not be expected to yield complete remissions, it is possible that they will prolong survival in some patients. Furthermore, data from clinical studies in oncology show a clear promise on their role in the anti-cancer armamentarium.

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References

Clinical guidance on PSIs in post-transplant malignancies


