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Malignancy in Kidney Transplant Recipients

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Abstract

Post-transplant malignancy morbidity and mortality are important limitations in kidney transplantation. The incidence of malignancy has been estimated at 20% after 10 years of chronic immunosuppression. The aetiology of post-transplant malignancy is multifactorial, with the increased risk for malignancy in transplant recipients correlating with overall exposure to immunosuppression. Strategies to understand and minimize the risk of developing malignancy in the transplant population are needed. Calcineurin inhibitors (CNIs) have been linked with post-transplant malignancies, while mammalian target of rapamycin (mTOR) inhibitors have shown antineoplastic activities. The dual efficacy of sirolimus as an immunosuppressive and antitumour agent has been demonstrated experimentally and clinically. Clinical studies have demonstrated a lower incidence of new malignancies after renal transplantation in recipients receiving immunosuppression with mTOR inhibitors compared with CNIs. Therapeutic protocols involving mTOR inhibitors may protect an allograft from immunological rejection, while at the same time addressing the problem of cancer in this high-risk population. Newer sirolimus analogues, such as temsirolimus, have become a focus in pure oncological research and are being evaluated for antineoplastic effects on a variety of malignancies in clinical trials.

1. Incidence of Post-Transplant Malignancy

With improved long-term graft and patient survival, longer exposure to immunosuppressive agents, and a shift toward older transplant recipients,[1] the incidence of malignant tumours in transplant recipients has increased in the past decade. It is now the third leading cause of death in kidney transplant recipients.[2] In 2004, malignancy in the US was the cause of death in 7% of kidney transplant recipients.[3] Between 5 and 10 years post-transplantation, 14% of deaths are attributed to malignancy,[1] and this rate increases to 26% after 10 years.[4] In the next 20 years, malignancy is expected to surpass cardiovascular disease as the leading cause of death.[5] Thus, cancer represents a major cause of morbidity and mortality in patients who were otherwise successfully treated by organ transplantation.[6]

There are three types of post-transplant malignancies: malignancies transferred from the donor; recurrent pre-existing malignancies; and *de novo* malignancies.[7] Analysis of US registry data (1994–2002) reveals that the incidence of donor-related malignancies and deaths is extremely small. In kidney transplant recipients with a history of cancer, the incidence of recurrent malignancy is 2.3%, while the incidence of *de novo* malignancy is

7.8%; in recipients without a history of cancer, the rate is 2.8%.[7] Post-transplant mortality associated with *de novo* cancers is high, with reports of 10-year patient survival of 93% for patients with no malignancy and 57% for patients with any malignancy.[8]

The rates for most *de novo* malignancies in kidney transplant recipients without a history of cancer are 2- to 3-fold higher than those of the general population.[9,10] However, the incidence is 15-fold higher for kidney cancer and more than 20-fold higher for lymphomas, non-melanoma skin cancers and rare tumours such as Kaposi's sarcoma, with skin cancer having the highest incidence.[10] Analysis of US registry data reveals that at 3 years after kidney transplantation the cumulative incidence of non-skin carcinomas is 7.45% and that of skin carcinomas is 7.43%.[10] Data from the Australia and New Zealand Dialysis and Transplant Registry reveal that the risk of overall *de novo* cancer, excluding non-melanoma skin cancer and cancers known to cause end-stage renal disease (myeloma, kidney, urinary tract), was 3.27-fold higher in kidney transplant recipients than in the general population, whereas the risk was only slightly higher in end-stage renal disease patients before renal replacement therapy (1.16) and during dialysis (1.35).[9] A recent study using data from the Australia and New Zealand Dialysis and Transplant Registry (15 183 people who received a transplant from 1963 to 2004) found that the risk of overall *de novo* cancers was 2–3 times higher for transplant recipients than in the general population (standardized rate ratio = 3.2 for females and 2.6 for males).[11] The risk of *de novo* cancers was inversely related to age, with younger recipients experiencing the greatest risk compared with the general population, and this risk declining with age.[11] The risk of cancer in transplant recipients compared with the general population varied by site and across age groups, but, with the exception of breast and prostate cancer in those aged >55 years, was always elevated in transplant recipients (table I).[11]

Table I. Site-specific cancer risk for kidney transplant recipients, by age and sex, compared with the general population (reproduced from Webster et al.,[11] with permission)

Cancer site	Age at cancer diagnosis (y)											
	<35			35–44			45–54			≥55		
	O	E	SRR (95% CI)	O	E	SRR (95% CI)	O	E	SRR (95% CI)	O	E	SRR (95% CI)
Female												
Breast	4	1.28	3.12 (1.17, 8.31)	11	7.80	1.41 (0.78, 2.51)	30	19.23	1.56 (1.08, 2.21)	34	37.31	0.91 (0.65, 1.27)
Colorectal	3	0.22	13.51 (4.34, 4.61)	8	1.16	6.88 (3.44, 13.75)	18	4.91	3.66 (2.31, 5.82)	45	19.88	2.26 (1.69, 3.03)
Melanoma	6	1.90	3.17 (1.42, 7.04)	7	3.25	2.46 (1.23, 4.93)	18	4.90	3.88 (2.47, 6.08)	33	8.93	3.70 (2.63, 5.20)
Lung	0	0.04		0	0.38		8	1.97	4.06 (2.03, 8.11)	30	10.08	2.98 (2.08, 4.26)
Lymphoma[a]	19	0.51	37.30 (23.79, 58.48)	11	0.75	14.67 (8.13, 26.50)	16	1.61	9.95 (6.09, 16.24)	33	5.23	6.30 (4.48, 8.87)
Male												
Prostate	0	0.00		0	0.13		2	4.02	0.50 (0.12, 1.98)	43	47.87	0.90 (0.64, 1.20)
Colorectal	0	0.33		13	1.93	6.73 (3.91, 11.60)	11	8.67	1.27 (0.70, 2.29)	37	33.14	1.12 (0.81, 1.54)
Lung	1	0.08	11.81 (1.66, 83.83)	4	0.80	5.03 (1.89, 13.39)	13	5.45	2.39 (1.39, 4.11)	48	27.85	1.72 (1.30, 2.29)
Melanoma	10	2.13	4.69 (2.53, 8.72)	20	4.57	4.38 (2.82, 6.79)	23	8.34	2.74 (1.82, 4.12)	46	15.54	3.15 (2.38, 4.17)
Lymphoma[a]	25	1.09	23.03 (15.56, 34.09)	23	1.85	12.43 (8.26, 18.71)	31	3.42	9.06 (6.37, 12.88)	50	7.57	6.61 (5.01, 8.72)

a Lymphoma classified in the general and transplanted populations to include Hodgkin's and non-Hodgkin's lymphoma. Comparison is made only with incidence in the Australian general population, as comparable lymphoma data were not available in New Zealand.

E = expected number of incident cancers in Australian and New Zealand general population of the same age and sex distribution, occurring over the same calendar years; **O** = observed incident cancers, in ANZDATA cohort, between 1980 and 2002; **SRR** = standardized rate ratio.

2. Aetiology of Post-Transplant Malignancy

Risk factors for malignancy in kidney transplant recipients include older age, White race, history of cancer, longer duration of dialysis and longer exposure to post-transplant immunosuppressive drugs.[1,9-14] The increased incidence of post-transplant malignancies has been attributed to several factors, including impairment of immune surveillance and antiviral activity with long-term immunosuppression, chronic antigen stimulation of the graft, reactivation of latent oncoviruses, and the direct oncogenic effect of the immunosuppressive agents.[11,15] A study by Vajdic et al.[9] found that kidney transplantation was associated with a greater than 3-fold risk of cancers that occurred at 18 body sites and were of known or suspected viral aetiology. Examples of these include Kaposi's sarcoma (207-fold), Hodgkin's (4-fold) and non-Hodgkin's (10-fold) lymphoma, and mouth, genitourinary and other cancers, which are related to human herpes virus 8, Epstein-Barr virus (EBV) and human papillomavirus, respectively. This suggests an interaction between immunosuppression and viral infections in the aetiology of cancer.[9]

The role of immunosuppressive drugs in the development of post-transplant *de novo* malignancies was elucidated in several early clinical reports showing an association between reduction/discontinuation of immunosuppressive drug therapy and the regression of tumours.[1] Further studies showed that the incidence of cancer was correlated with the extent of immunosuppression, with a low-dose ciclosporin (cyclosporine) maintenance regimen associated with fewer malignancies than a normal-dose ciclosporin maintenance regimen.[12] While both ciclosporin and tacrolimus are associated with increased risk of malignancy, whether tacrolimus is safer than ciclosporin remains controversial because of conflicting data.[1,5]

3. Calcineurin Inhibitors

As an immunosuppressive agent, ciclosporin binds to the immunophillin cyclophilin A, inhibiting calcineurin phosphatase and subsequently blocking nuclear factor of activated T cells (NFAT) translocation into the nucleus. Ciclosporin also increases transforming growth factor (TGF)-β, a potent inhibitor of interleukin (IL)-2-stimulated T-cell proliferation.[16]

Initially, the oncogenic effects of ciclosporin were attributed to inhibition of T-lymphocyte-mediated immune surveillance (figure 1). However, based on previous observations that ciclosporin increases TGFβ expression, and that TGFβ promotes tumour cell invasion and metastasis, Hojo et al.[17] evaluated the direct cellular effects of ciclosporin in

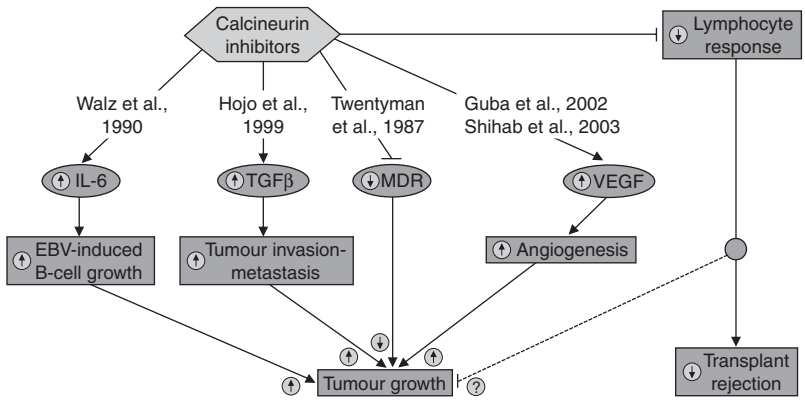

Fig. 1. Reported activities of calcineurin inhibitors (CNIs) related to cancer and transplantation.[17,20-23] Predicted effect in the presence of CNIs (circled arrows) [reproduced from Guba et al.,[24] with permission]. **IL** = interleukin; **EBV** = Epstein-Barr virus; **MDR** = multidrug resistance; **TGF** = transforming growth factor; **VEGF** = vascular endothelial growth factor; ↑ indicates increased; ↓ indicates decreased; **?** indicates unknown.

an *in vitro* epithelial cell line. They demonstrated that ciclosporin induced an invasive phenotype in nontransformed adenocarcinoma cells via a TGFβ-dependent mechanism, pointing to a direct neoplastic effect of ciclosporin.[17] Furthermore, ciclosporin promoted neoplastic progression of several tumour lines, in T cell-, B cell- and natural killer (NK) cell-deficient severe combined immune deficiency (SCID)-beige mice, confirming an effect independent of host immunity. This effect was prevented with TGFβ blockade.[17] Similarly, tacrolimus enhanced the expression of TGFβ both *in vitro* and *in vivo* and promoted renal cancer cell pulmonary metastases in immunocompetent and immunodeficient mice.[18] In another study, tacrolimus was shown to increase the proliferation rate of human hepatoma cells.[19]

Other *in vivo* studies using various mouse models have shown that ciclosporin also enhances tumour growth (colon adenocarcinoma) by promoting angiogenesis and increasing expression of vascular endothelial growth factor (VEGF).[20] Upregulation of VEGF expression with ciclosporin treatment *in vivo* has been confirmed by Shihab and colleagues.[21] Ciclosporin has also been shown to upregulate another cytokine, IL-6, which fosters B-cell activation and growth of EBV-transformed B cells. IL-6 may be involved in the development of post-transplant lymphoproliferative disease (PTLD) that is observed with ciclosporin treatment.[22] Thus, it appears that ciclosporin promotes tumour growth through both direct and indirect mechanisms. The increased risk of malignancy associated with ciclosporin may be related to promotion of synthesis of cytokines that regulate processes promoting tumour growth, metastasis and angiogenesis, in addition to other possible tumour-promoting mechanisms (figure 1).[24]

4. Corticosteroids

The use of corticosteroids in solid organ transplantation has been widespread for the past 40 years – almost always in combination with other immunosuppressive agents. As a result, there is a paucity of data regarding the pro-oncogenic or antioncogenic role of corticosteroids in organ transplant recipients. In the nontransplant setting, where patients have received corticosteroids without other confounding immunosuppressive agents, there is a suggestion of the pro-oncogenicity of corticosteroids to increase the risk of malignancy, especially skin cancers.[25,26] Therefore, corticosteroids could be implicated in increasing the risk of malignancy in organ transplant recipients.

5. Antimetabolites

5.1 Azathioprine

Azathioprine is a purine analogue that inhibits purine synthesis and therefore interferes with RNA metabolism and synthesis. The probable pro-oncogenic effects of azathioprine have not been definitively proven, but there is a suggestion that azathioprine could promote oncogenesis through a number of potential mechanisms. Azathioprine has been shown to increase the incidence of UV radiation-induced skin cancers in mice.[27] Although there is a paucity of epidemiological evidence for the pro-oncogenic effect of azathioprine, there is evidence for an increase in post-transplant malignancy associated with azathioprine in the pre-ciclosporin era from the Penn Registry.[28] Certainly, azathioprine has been shown not to be as potent a pro-oncogenic agent as the calcineurin inhibitors (CNIs), especially ciclosporin.[29,30]

5.2 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid – a potent immunosuppressive antimetabolite. MMF is an inhibitor of inosine monophosphate dehydrogenase, which is essential for T and B lymphocyte proliferation. There are confounding data on both the antioncogenic and pro-oncogenic effects of MMF. Some data suggest MMF may increase tumour cell invasiveness,[31] while conflicting data suggest that MMF may prevent adhesion receptor-dependent tumour progression.[32] There has been no epidemiological study showing either an increased or decreased risk of malignancy in patients on MMF compared with

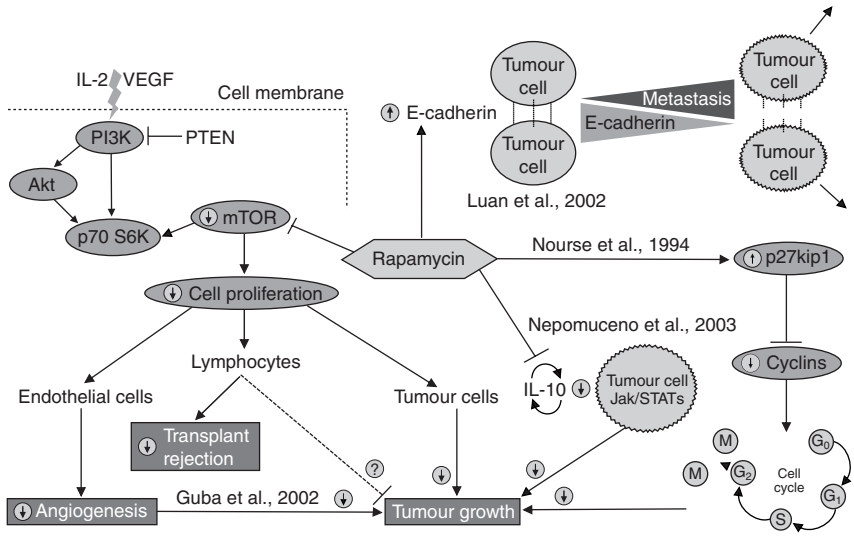

Fig. 2. Reported activities of rapamycin related to cancer and transplantation.[20,37-39] Predicted effect in the presence of rapamycin (circled arrows) [reproduced from Guba et al.,[24] with permission]. **IL** = interleukin; **mTOR** = mammalian target of rapamycin; **PI3K** = phosphatidylinositol-3-kinase; **PTEN** = phosphatase and tensin homolog deleted from chromosome 10; **STAT** = signal transducers and activators of transcription; **VEGF** = vascular endothelial growth factor; ↑ indicates increased; ↓ indicates decreased; **?** indicates unknown.

azathioprine, with MMF proving itself to be a potent and effective immunosuppressant.[33]

6. Induction Agents (Biological Agents)

There is a significant body of literature showing that lymphocyte-depleting polyclonal antibodies increase the risk of malignancy. Specifically, there is an increased risk of PTLD and skin cancers with induction agents. In comparing the polyclonals, there is suggestion that thymoglobulin may have a higher relative risk of malignancy than the antithymocyte globulin (ATG) Fresenius.[34] An analysis of the Scientific Registry of Transplant Recipients database found no difference in the polyclonal antibodies, all having an equally high relative risk of post-transplant malignancy.[35]

The non-lymphocyte-depleting anti-CD25 monoclonal antibodies have not been shown to increase malignancy rates in multiple studies. These monoclonal antibodies have activity restricted to activated T cells and monocytes/macrophages. This reduces the number of circulating T lymphocytes expressing IL-2 receptors, but the total number of lymphocytes is unaffected.[36]

7. Mammalian Target of Rapamycin Inhibitors

Sirolimus, a macrocyclic lactone, displays a different mechanism of immunosuppressive action from that of ciclosporin, forming a complex with FK binding protein complex (FKBP) 12 and binding with high affinity to the mammalian target of rapamycin (mTOR). mTOR controls the phosphatidylinositol-3-kinase (PI3K)/Akt signalling pathway, which plays a pivotal role in cell growth and survival – its dysregulation has been described in a variety of cancer cells (figure 2). PI3K is activated by growth factor/cytokine-triggered receptors, leading to phosphorylation of Akt and subsequent downstream effectors. Inhibition of mTOR by sirolimus, or its derivatives temsirolimus and everolimus, downregulates p70 S6 kinase activity and subsequent translation of specific mRNAs required for cell-cycle progression from the G1 to S phase, effectively blocking IL-2 stimulation of lymphocyte proliferation (figure 2).[15,16,24] Interestingly, the CNI tacrolimus also binds to FKBP12; however, the complex forms a ternary complex with calcineurin,

resulting in an immunosuppressive mode of action similar to that of ciclosporin.[16]

In its early development, sirolimus, initially discovered as an antifungal antibiotic, was recognized to have anticancer activity (at high doses) in murine models,[40] as well as an immunosuppressive effect, which while detrimental in fighting infections proved to be beneficial in transplantation.[41] After its approval for maintenance immunosuppression in 1999, sirolimus was found to have a striking antitumour effect in experimental models of renal cell carcinoma. *In vitro*, sirolimus converted murine renal cancer cells from an invasive to a noninvasive phenotype, augmenting E-cadherin at cell-to-cell contacts, thereby reducing spread and metastatic progression, as well as reducing cyclin D1 and increasing p27 kip 1, which inhibit G1 to S transition (figure 2),[37] potentially slowing tumour growth.[38]

In several murine models of renal cancer cell tumour progression, sirolimus has been shown to constrain tumour growth and metastatic progression and prolong survival, even in the presence of ciclosporin.[37] Further mechanistic studies examining human renal cell carcinoma pulmonary metastasis in SCID-beige mice have demonstrated the antitumour efficacy of sirolimus with targeted reduction of the tumour promoting cytokines TGFβ and VEGF-A.[42] In contrast to ciclosporin, sirolimus has been shown to have an antiangiogenic effect, via downregulation of VEGF,[20] as well as an antivascular effect, which may contribute to its antineoplastic action through an indirect mechanism.[43] Blockade of mTOR may also have an inhibitory effect on aberrant activity of upstream molecules, such as Akt, which occurs in some cancers (e.g. Kaposi's sarcoma[44] from loss of regulation by PTEN [phosphatase and tensin homolog deleted from chromosome 10]). Everolimus has been shown to have an antiproliferative effect on EBV-transformed B lymphocytes, by reducing IL-10 secretion, thereby demonstrating therapeutic potential for prevention or treatment of PTLD.[45] Thus, mTOR inhibitors have been shown to have potent antitumour effects in several experimental tumour models[16] and these effects may be mediated via direct and indirect mechanisms.

The immunosuppressive and antitumour effects of sirolimus were studied simultaneously in a mouse tumour transplant model. Immunosuppressive doses of sirolimus were effective in preventing allograft rejection and inhibiting tumour growth, as well as opposing the tumour-enhancing effects of ciclosporin. In contrast, ciclosporin treatment resulted in death of mice due to advancing tumours, albeit with a functioning graft.[6]

8. Effects on Malignancy with Mammalian Target of Rapamycin Inhibitors in Kidney Transplant Recipients

The dual action of sirolimus has been revealed in case reports and early clinical studies in kidney transplant patients. Conversion from ciclosporin to sirolimus in renal transplant patients with cancer showed complete regression of Kaposi's carcinoma lesions[46,47] and regression of PTLD,[48,49] while maintaining kidney graft function. These studies suggest switching from ciclosporin to sirolimus may be a potential treatment for malignancy in transplant patients without increasing the risk of graft rejection.

Analyses of 2-year malignancy rates in randomized, multicentre studies revealed a significantly lower incidence of skin cancer in patients treated with sirolimus in combination with ciclosporin and a reduced incidence of total cancers with sirolimus and early ciclosporin withdrawal.[50] Similarly, a single-centre study of 1008 renal transplant recipients followed for a mean of approximately 5 years found that a combination regimen of sirolimus and ciclosporin plus corticosteroid resulted in a reduction in the incidence of non-melanoma skin cancers, the most common malignancies, to 2.1% from the 7% previously reported with other immunosuppressive regimens.[14] In the same study, the sirolimus-based regimen was associated with a 3.73-fold increase in the incidence of PTLD and a 3.58-fold increase in the incidence of renal cell carcinoma, compared with the general population – much lower than the increased rate of these two cancers pre-

viously reported with tacrolimus-based therapy (i.e. 27-fold increase for PTLD and 8-fold increase for renal cell carcinoma).[14]

Retrospective analyses of the OPTN/UNOS (Organ Procurement and Transplantation Network/ United Network for Organ Sharing) registry showed a significantly lower incidence of new malignancies after renal transplantation in recipients receiving immunosuppression with an mTOR inhibitor alone, or an mTOR inhibitor (sirolimus/everolimus) in combination with a CNI (ciclosporin/tacrolimus), compared with a CNI alone at 963 days post-transplant (0.6% vs 1.8%; p = 0.041, and 0.6% vs 1.8%; p < 0.0001, respectively).[13] Sirolimus/everolimus maintenance immunosuppression was associated with a 61% reduced risk of developing any *de novo* malignancy (relative risk [RR] 0.39; 95% CI 0.24, 0.64; p = 0.0002) and a 56% reduced risk of developing a non-skin *de novo* solid cancer (RR 0.44; 95% CI 0.24, 0.82; p = 0.0092) compared with ciclosporin/tacrolimus maintenance immunosuppression.[13] Recent 5-year randomized, controlled trial data from 430 renal transplant recipients demonstrated that patients receiving sirolimus-corticosteroid therapy following early (3-month) ciclosporin withdrawal had a lower relative risk of developing skin cancer (RR 0.346; 95% CI 0.227, 0.526; p < 0.001) and a reduced incidence of non-skin cancers (3.7% vs 8.4%; p = 0.043) compared with patients receiving sirolimus-corticosteroid combined with continuous ciclosporin therapy.[51] The median time to a first skin carcinoma was also delayed in patients receiving sirolimus-based ciclosporin-free therapy, compared with patients receiving sirolimus-corticosteroid combined with continuous ciclosporin therapy (491 vs 1126 days; p = 0.007).[51]

Therapeutic protocols involving mTOR inhibitors may simultaneously protect an allograft from immunological rejection and address the problem of cancer in this high-risk population.[24] Since post-transplant malignancies develop frequently and within relatively short time spans, compared with cancers in the general population, they provide a unique opportunity to study the neoplastic process and analyse treatment in a human model.[7]

9. Mammalian Target of Rapamycin Inhibitors in the Cancer Field

mTOR inhibitors are being clinically developed both as immunosuppressants for prevention of allograft rejection and as novel therapeutics in the fight against human cancer. Temsirolimus is being tested clinically as a pure oncological agent in phase I, II and III trials, on a variety of different cancers. To date, temsirolimus has shown promising results in phase II trials in patients with breast cancer,[52] relapsed mantle cell lymphoma,[53] glioblastoma multiforme[54] and advanced refractory renal cell carcinoma.[55]

A recent phase III trial compared temsirolimus with interferon (IFN)-α in patients with metastatic renal cell carcinoma and poor risk factors.[56] Patients with no prior systemic therapy were enrolled in this open-label study if they had 3 of 6 risk factors (the 5 Motzer criteria and >1 metastatic disease site). Patients were randomized (1 : 1 : 1) to arm 1, IFNα up to 18 million units subcutaneously three times weekly (n = 207); arm 2, intravenous temsirolimus 25 mg once weekly (n = 209); or arm 3, intravenous temsirolimus 15 mg once weekly + IFNα 6 million units subcutaneously three times weekly (n = 210). Patients in the single-agent temsirolimus group had a significantly longer survival compared with patients in the IFNα group (10.9 vs 7.3 months; p = 0.0069); however, there was no difference in survival between the IFNα group and the group receiving both IFNα and temsirolimus (7.3 vs 8.4 months; p = not significant).

10. Conclusions

With over 90 000 renal transplant recipients living in the US and a malignancy rate of 26% after 10 years of immunosuppression, the burden of post-transplant malignancy is significant and an important concern for transplant practitioners. CNIs continue to be one of the most commonly used immunosuppressive agents and have been implicated in the aetiology of post-transplant tumours. mTOR in-

hibitors, such as sirolimus and everolimus, while less frequently used, have been shown to have potent immunosuppressive activity in transplant patients, as well as exhibiting significant antineoplastic properties. Renal transplant recipients receiving immunosuppression with mTOR inhibitors have a lower incidence of new malignancies compared with recipients receiving CNIs. Newer generation mTOR inhibitors, such as temsirolimus, are being developed as antineoplastic agents in oncology patients and may have the potential of playing a dual role as both immunosuppressive and antineoplastic agents in renal transplant patients.

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