Renal Transplantation and Cancer: Focus on Immunosuppressive Therapy

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Abstract

Posttransplant malignancy is currently considered one of the unavoidable long-term side effects of chronic immunosuppressive therapy and, in recent years, cancer has been recognized as a major limitation of organ transplantation results. In this review, we present an analysis of the current literature and aim to clarify the multiple epidemiologic, clinical, and biological facets of the association between immunosuppressive therapy and malignancy in organ transplant recipients. The risk of malignancy is elevated in solid-organ transplant recipients in comparison with the general population. Epidemiologic data reveal that length of exposure to immunosuppressive therapy and its intensity are clearly related to posttransplantation malignancy risk, and that once cancer has developed, more intense immunosuppression can translate into more aggressive tumor progression in terms of accelerated growth and metastasis and lower patient survival. Several pathogenic factors are responsible for the relation between immunosuppressive therapy and posttransplantation malignancy. Two, and probably the most relevant indirectly, immunosuppressive drugs greatly increase posttransplantation malignancy risk by impairing cancer surveillance and facilitating the action of oncogenic viruses. However, the direct pro- and anti-oncogenic actions of immunosuppressors also play an important role. The cancer-promoting effect of calcineurin inhibitors, independently of depressed immunosurveillance, has been demonstrated in recent years, and currently only mammalian target of rapamycin inhibitors have simultaneously shown immunosuppressive and antitumoral properties. Reports of the initial results of the reduced incidence of de novo *cancer in organ transplant recipients under mammalian target of rapamycin inhibitor therapy strongly indicate separate pathways for pharmacologic immunosuppression and oncogenesis. The role of mammalian target of rapamycin inhibitors has been firmly established for posttransplantation Kaposi's sarcoma, but should be clarified in the management of patients with other posttransplant malignancies, and should be followed by long-term results and studies in non-kidney recipients. Prevention of posttransplant malignancy morbidity and mortality must be a main endpoint in solid-organ transplant programs, and the choice and management of immunosuppres-*

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sive therapy in each phase of transplantation plays a central role in this objective. Hope lies in several approaches: (i) the various efforts that are being directed to monitoring the minimal doses of immunosuppressants required to achieve allograft survival and to avoiding the secondary effects related to over-immunosuppression; (ii) the search for some degree of tolerance; (iii) the new clinical data about mammalian target of rapamycin inhibitor results in transplanted patients. **(Trends in Transplant 2007;1:3-14)**

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Key words

Introduction

Organ transplantation is the optimal therapy in most situations of end-stage organ failure. However, this transplantation requires the use of immunosuppressive drugs that decrease the risk of acute rejection and improve graft and patient survival. The advances in organ transplant research have been focused on this point of view, acquiring good acute-rejection rates and excellent graft and patient survival. However, immunosuppressive therapy is also associated with chronic allograft nephropathy and cardiovascular disease, as well as development of malignant disease. The chronic impairment of immune function and the direct secondary effects of exposure to these drugs are responsible for these downside effects.

As long-term survival with functioning allograft increases, more patients will be at risk of developing malignancies. Cancer is thus a growing concern in the scientific community and continuous evaluation of the available evidence on this topic is essential.

This article aims to systematically review the available information on the issue of immunosuppressive therapy and malignancy in organ transplant recipients, focusing on the experimental and clinical data on the pro- and anti-oncogenic effects of different immunosuppressive drugs.

Epidemiology of malignancy in renal transplant recipients

The perception of malignancy as a complication of organ transplantation emerged at an early date[1-5], and one of the major contributors to the discovery of this association was Israel Penn (1930-1999), through what is currently known as the "Israel Penn International Transplant Tumor Registry" (http://www.ipittr.uc.edu/Home.cfm).

Large registries are the best source of information about malignancy incidence rates. However with few exceptions[6-9], many others of these registries are subject to several limitations, e.g. voluntary contribution to the registry[10,11], incomplete number of organ transplant recipients[11,12], non inclusion of some types of tumor such as non-melanoma skin cancers (NMSC)[12], record of only first-cancer cases[10,13,14], or short follow-up periods[15,16]. Besides, the retrospective and the underestimated frequency of posttransplant malignancy of the single-centre studies, the enormous tumor rate variations of rare tumors, and the lack of sufficient number of patients to detect significant differences in patient survival or malignancy incidence, complicate the interpretation of clinical data.

As a result of these limitations, the large number of studies published on the subject shows wide variability in malignancy rates after organ
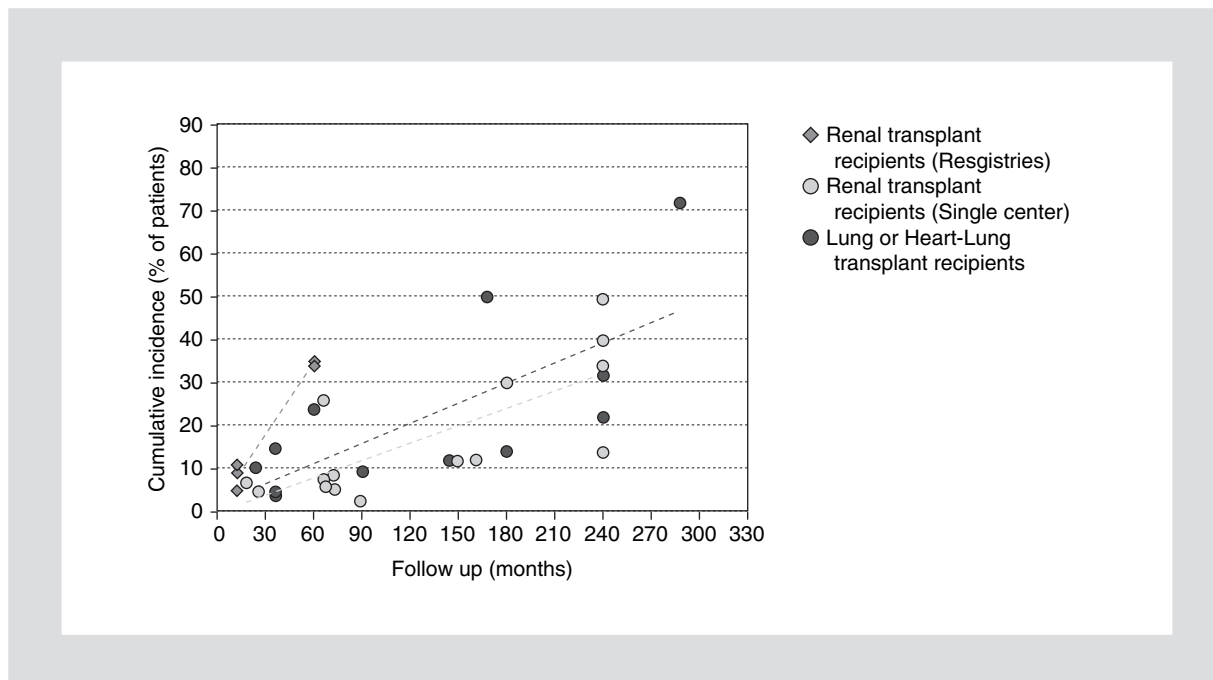
Figure 1. *Incidence of cancer in organ transplant recipients reported by different registries and single center studies.*

transplantation (Fig. 1). It could also explain the disagreement in occurrence of cancer after kidney transplantation between the studies of Kasiske, et al.[15] and the Australian and New Zealand Data Registry (ANZDATA)[17], with a three-year cumulative incidence of 14.9 and 13%, respectively, and the previous analyses of the Collaborative Transplant Study (CTS) or the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), 4.7 and 3.9%, respectively, with the same length of follow-up[16]. However, some of the differences observed in malignancy incidence rates may also be due to different follow-up times, since the duration of immunosuppression has been considered to be one of the most important factors in the increase in the incidence of malignancies[18-21].

The elevated risk and incidence of malignancy in organ transplant recipients have a tremendous clinical impact. Malignancy causes a substantial proportion of late mortality after transplantation, ranging between 10 and 47%, mainly depending on the duration of posttransplant follow-up[10,22-26]. In most studies, the primary cause of mortality is undoubtedly cardiovascular disease,

although malignancy is gaining ground as long-term survival is achieved in a greater number of transplant recipients. Indeed, malignancy is the first cause of death in the ANZDATA registry[10], and is usually among the first three causes of death (together with cardiovascular and infectious diseases) in other registries[22-26]. In summary, malignancy is nowadays one of the major factors limiting life expectancy in organ transplant recipients.

Carcinogenesis and immunosuppressive therapy

The cancer pathogenesis in organ transplant recipients is difficult to assess because of the mixture of pathogenic factors in these patients. The presence of environmental and genetic risk factors (common to the general population) and the complex interaction established between the effect of depressed immunosurveillance, the action of pro-oncogenic viruses, and possibly direct carcinogenic effects of immunosuppressive drugs, converge in transplant recipients. The final effect of these factors is manifested by an increased risk of malignancy in these patients. One of the most

solid arguments for this association was reported by Dantal, et al. in a prospective, open, randomized trial of two cyclosporin A (CsA) regimens (low-dose and normal-dose) in renal transplant recipients, where malignancy was more frequent in the normal-dose group in 66 months of follow-up[26]. In addition, several retrospective studies have also been able to show increased malignancy rates associated with more intense exposure to an immunosuppressive drug[27-29] or utilization of a stronger immunosuppressive regimen[30-32].

It is well known that more intense immunosuppression is used to prevent and treat allograft rejection in organs other than the kidney[33-35], and this phenomenon is correlated with a progressive increase in malignancy rates in kidney, liver, pancreas, heart, lung, and combined heart-lung transplantation (Fig.1). This is translated not only into an increased malignancy risk, but also into more aggressive tumor progression in terms of accelerated growth and metastasis[36], and lower patient survival[37-40]. In contrast, a reduction of immunosuppression might have a positive impact on the clinical course of the tumor and on the prognosis for survival, at least in certain types of cancer.

Cancer immunosurveillance

The definitive evidence about the influence of immunosuppressive therapy in cancer surveillance came from studies showing that lymphocytes in mice not only protect the host against the formation of chemically induced cancers, but also prevent the development of spontaneous epithelial tumors. Immunosurveillance is also involved in defense against the early steps of the metastatic processes, which include vascular emboli, lymphatic invasion, and perineural invasion (collectively referred to as VELIPI). Recent data suggests that tumors without evidence of VELIPI contained significantly more memory T-cells[41], and that prolonged survival and the absence of pathologic signs of early metastatic invasion was associated with increased levels of mRNA for products and markers of Th1 effector T-cells[41].

If we compare between renal transplant recipients and populations under dialysis, or even better on the waiting list, like immunosuppressive therapy, end-stage renal disease and uremia are also associated with immune system abnormalities, which could increase susceptibility to malignancies and confound the analysis[42,43]. However, an assessment of 13,077 renal transplant recipients from 1980 to 2003 versus 33,820 patients undergoing dialysis in the same period in Australia and New Zealand showed numerically higher standardized incidence ratios for a wide range of nonviral tumors, including melanoma, cancers of the digestive and respiratory tract, leukemia, and tumors of bone and soft tissues in transplant recipients[44]. Even kidney cancer, which is strongly related to uremia[45,46], is more common in transplant recipients than in patients on the waiting list[7,15].

Virally induced malignancies

Several analyses from Australia, New Zealand, the USA, Ireland, the Nordic countries, and Japan in transplant recipients have a sufficient number of patients and duration of follow-up to show an increased risk for a wide range of malignancies with no known viral etiology. However, compared with the general population, organ transplant recipients have been reported to have greater relative risk ratios for a broad subset of tumors with no apparent viral origin (Fig. 2)[6-8,13-15,44,47-49], and a limited number of viruses have been related to different malignancies in transplant recipients and the general population (Table 1). According to the mechanism through which these viruses induce tumors, they can be grouped into two categories: direct oncogenic viruses[50] (possibility to modify proliferation/anti-proliferation pathways of the host-cell as a strategy for maintaining their own replication[51], e.g. deactivate tumor-suppressor gene proteins such as retinoblastoma and p53[52]) and viruses that are only indirectly carcinogenic[50] (their presence increases the probability of specific types of malignancy several fold, although they are not able to cause malignant transformation directly). Other onco-

genic factors probably also contribute to multi-step carcinogenesis.

The effect of depressed immunosuppressive therapy in immunosurveillance produces in transplant recipients an increase in the risk of infections and their persistence, and in the probability that the transformed cell will escape, allowing cancer cells to proliferate and clonally expand, resulting in a substantial increase in the relative risk of these malignancies (Fig. 2).

Pro- and anti-oncogenic effects of immunosuppressive drugs

Nowadays, clinical data are not sufficient to discriminate between immunosuppressive and direct cancer-promoting effects of different immunosuppressive drugs. In contrast, there is growing experimental evidence of the different oncogenic effects of immunosuppressive drugs, which could be of great value in assessing this question, and of the relevance in the clinical setting.

Biologic immunosuppressive agents

Lymphocyte-depleting antibodies have been shown, as a group, to clearly increase the risk of malignancy, mainly of viral-induced cancers. There are very little data from direct comparisons between these drugs, and most studies do not analyze polyclonal agents individually[35,53,54]. A single-center study showed differences in lymphoma incidence and delay to cancer diagnosis between two different antithymocyte globulins (ATG). Thymoglobulin carried a higher relative risk (RR: 2.16) of malignancy, mainly lymphoma, than did ATG-Fresenius[55]. This initial finding has recently been corroborated by a study that analyzed the incidence of non-Hodgkin's lymphoma (NHL) according to type of induction used in 112,122 renal-transplant patients reported to the CTS database[56].

The underlying mechanism of these differences is not known. Their variable oncogenic ac-
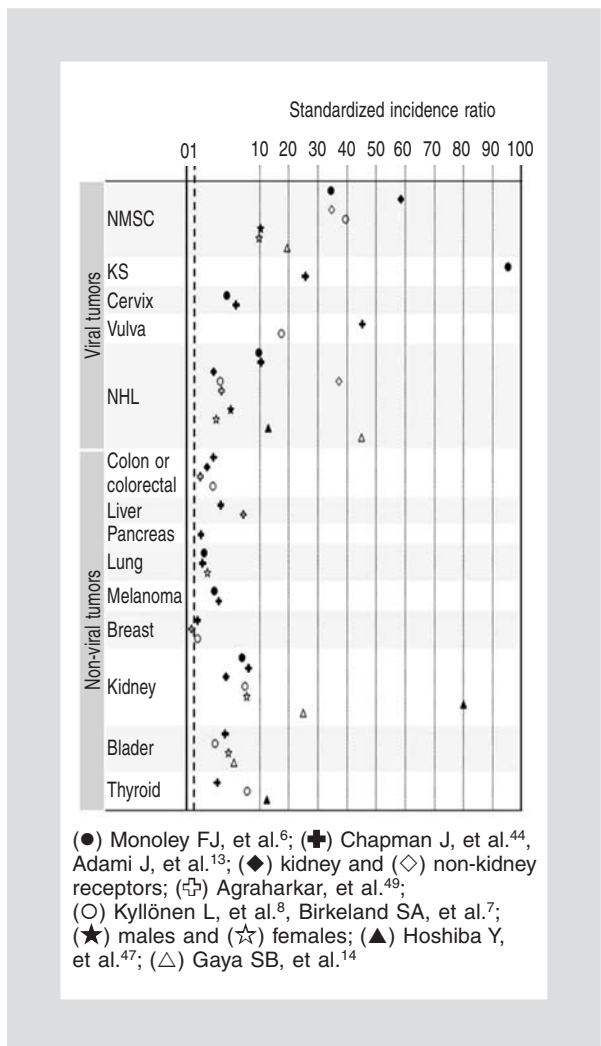
Figure 2. *Standardized incidence ratios for tumors of viral and non-viral origin.*

tivity can probably be explained by differences in the range of activity of the different polyclonal and monoclonal antibodies against lymphocyte surface antigens. ATG-Fresenius displays a significantly narrower spectrum of activity against lymphocyte antigens than do Atgam and Thymoglobulin[57], whereas OKT3 has a powerful T-cell depleting activity and also blocks the function of killer T-cells[58].

The only antibodies that show immunosuppressive efficacy in reducing acute rejection rates[59,60] (and there is no consistent evidence that they increase malignancy risk[35,53,54,56,59,60]) are non-lymphocyte-depleting anti-CD25 monoclonal antibodies.

Table 1. Oncogenic viruses and related malignancies

Virus	Malignancy
Human papillomaviruses	Cervical carcinoma Non-melanoma skin cancer Anogenital cancer
Human polyomaviruses (BKV, JCV, SV40)	Mesotheliomas Brain tumors
Epstein-Barr virus	B-cell lymphoproliferative diseases Nasopharyngeal carcinoma
Kaposi's sarcoma Herpesvirus (HHV8)	Kaposi's sarcoma Primary effusion lymphomas
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
Human T-cell leukemia Virus-1	T-cell leukemia
Helicobacter pylori	Gastric carcinoma

Glucocorticoids

Glucocorticoids (GC) have been extensively used in organ transplantation and are an essential part of most immunosuppressive regimens, but there are few epidemiologic data on their pro-oncogenic role in organ transplant recipients, although in non-transplanted patients without administration of other immunosuppressive drugs than GC, they have been related to an increased risk of malignancy, mainly of NMSC[61].

Glucocorticoids have been proposed to play a dual role in oncogenesis. Through a direct pro-oncogenic action in cells or by facilitating tumor cell escape from immunosurveillance, GC could significantly contribute to the increased malignancy risk observed in organ transplant recipients. For instance, recent data have demonstrated antiapoptotic and proliferating-promoting effects of GC in carcinoma cells from a wide variety of tumors (recently reviewed in ref. 134)[61], or other characteristics of GC such as enhancing tumor cell resistance[61,62], inactivating B and T lymphocytes (including activated killer T-cells[63]), reducing the expression of major histocompatibility (MHC) class I antigen *in vivo*[64], and decreasing immunosurveillance even at very low doses[65].

Antimetabolites: azathioprine and mycophenolate mofetil

Azathioprine (AZA) could directly promote cancer through several mutagenic mechanisms, directly or by synergism with UV light[66,67], inducing chronic oxidative stress and mutagenic DNA lesions.

The data on the pro- or anti-oncogenic activity of mycophenolate mofetil (MMF) are conflicting. On the one hand, it has been associated with a potential enhanced tumor-cell invasiveness[68] and a mutagenic effect *in vitro*[69], while on the other hand, it has been related to possible prevention of adhesion receptor-dependent tumor dissemination[70,71]. In addition, MMF has been suggested to enhance the anti-herpes activity of acyclovir and ganciclovir, which could be of value in preventing the development of Epstein-Barr virus-induced posttransplant lymphoproliferative disease (PTLD)[72].

Several clinical studies have tried to clarify the pro- or anti-oncogenic role of MMF, finding similar overall cancer incidence rates in heart transplant recipients[73] and no significant differences in the incidence of skin cancer in renal trans-

plant recipients[74] or risk of developing PTLD[16,75], although a data analysis of the CTS population and the Scientific Registry of Transplant Recipients showed that MMF therapy was associated with a decreased risk of PTLD and of any cancer[16,54].

Calcineurin inhibitors

These drugs have, apart the immunosuppressive effect on calcineurin inhibition[76], pleiotropic effects, enhancing production of transforming growth factor β1 (TGF-β)[77-79] (implicated in the acquisition of tumor invasiveness and metastatic spread[80,81], acting on the host to suppress antitumor immune responses, enhancing extracellular matrix production and augment angiogenesis[81,82]). These facts have been shown by the studies of Hojo M, et al[83-85] and other groups[86], with similar findings with CsA and tacolimus[79], although in the case of tacrolimus the effect was exhibited only with higher doses than the drug dosage required to promote experimental allograft acceptance[87]. Other pleiotropic effects would be the increase of expression of vascular endothelial growth factor (VEGF), responsible for enhancement of tumor angiogenesis[88], and the inhibition of p53-induced apoptosis in cancer cells[89-91].

Historically, AZA-based regimens have generally shown higher malignancy rates and a lower mean time to tumor development than CsA[8,28,30,92-94], although some studies found no significant differences[8,32]. In the comparison of the two calcineurin inhibitors (CNI) in patients without induction therapy, the cumulative PTLD incidence was lower in CsA-treated patients than in tacrolimus-treated patients[53,95,96], but the results seem to differ in non-PTLD cancer, without differences in solid tumors between CsA- and tacrolimus-based regimens[96-98].

A possible explanation is that the greater immunosuppressive effect of tacrolimus is manifested by a higher rate of PTLD, a virally induced malignancy, which is highly dependent on the overall level of immunosuppression induced.

However, the lower pro-oncogenic effect of tacrolimus[79] may be able to counterbalance its greater immunosuppressive effect, thus equalizing or reducing the rates of solid tumors associated with tacrolimus in comparison with CsA.

Mammalian target of rapamycin inhibitors

Role of the mTOR pathway in cancer

The last few decades of research have placed the mammalian target of rapamycin (mTOR) as a central element at the crossroads of the multiple signaling pathways that control cell growth. The mTOR signaling plays a role in various growth-related processes[99]: translation, ribosome biogenesis, macro-autophagy, transcription of many genes involved in metabolic and biosynthetic pathways, and metabolism.

All signaling components upstream and downstream of mTOR are frequently altered in a large number of human tumors. Indeed, preclinical studies suggest that the sensitivity of tumors to mTOR inhibitors may correlate with aberrant activation of the PI3K-Akt-mTOR pathway and/or with altered expression of cell cycle regulatory or anti-apoptotic proteins. Under this rationale, sirolimus (Rapamune®, Wyeth, USA) and its derivatives temsirolimus (CCI-779, Wyeth, USA), Everolimus (RAD-001, Novartis Pharma AG, Switzerland) and AP-23573 (Ariad Pharmaceuticals, USA) are currently being evaluated in clinical trials as cancer treatments. The results show that mTOR inhibitors may induce prolonged stable disease and even tumor regression in a subset of patients[100].

The mTOR inhibitors and cancer in organ transplantation

After mTOR inhibitors were introduced in organ transplantation, several studies aimed to demonstrate their dual role as immunosuppressors and antitumoral drugs. Guba, et al.[88] and Luan, et al.[84] demonstrated *in vivo* that sirolimus

(SRL) inhibited tumor growth and the metastatic process through an anti-angiogenic mechanism interfering with VEGF signaling. Kohel, et al.[85] showed that SRL simultaneously protected allografts from rejection and inhibited tumor progression, while CsA promoted cancer at doses even lower than the optimal immunosuppressive doses. Importantly, the deleterious effect of CsA was abrogated by simultaneous administration of SRL in the different *in vitro* and *in vivo* experimental models previously described[84,85,88,101].

Since the introduction of SRL in the clinical scenario, *de novo* cancer-incidence rates in transplant recipients under SRL therapy seem to confirm experimental data. Two randomized controlled trials comparing CsA and SRL-based regimens, using AZA or MMF and steroids in renal allograft recipients (n = 161), showed a 5% *de novo* cancer incidence in the CsA group versus 0% in the SRL group after a two-year follow-up[102]. Two further randomized controlled trials (n = 1295 patients) examined the continuous combination of CsA and SRL with steroids, and compared this regimen with a combination of CsA, steroids, and AZA or placebo. Two years posttransplantation, the incidence of skin cancer was significantly lower in patients receiving SRL and CsA than in those receiving placebo. However, the cumulative incidence of all cancers did not differ between the groups[102].

The malignancy related five-year follow-up results of another randomized controlled trial have recently been reported by Campistol, et al.[103]. In this study, enrolled patients (n = 525), initially treated with a triple regimen of CsA, SRL, and steroids, were randomly assigned at three months to remain on the initial regimen or to have CsA withdrawn. This latter strategy reduced the relative risk of skin cancer (RR: 0.35) and delayed the median time to the development of a first skin carcinoma compared with the group that remained on CsA. The incidence of non-skin malignancies at five years after renal transplantation was also reduced in patients who received CNI-free therapy after CsA withdrawal, compared with patients who received SRL therapy combined with CsA[103]. A last randomized controlled trial that assigns stable renal-transplant patients to an SRL-based, CNI-free conversion regimen (n = 555) or to CNI continuation (n = 275) assesses this question. At 18 months after randomization, overall malignancy rates were significantly lower among SRL-conversion patients compared with CNI-continuation patients, as were rates for NMSC (basal cell carcinoma and squamous cell carcinoma) and other malignancies, except for PTLD[104]. Finally, a retrospective, registry based study (UNOS database) demonstrated that maintenance immunosuppression with TOR inhibitors is associated with a significantly reduced risk of developing any posttransplant *de novo* malignancy or non-skin solid malignancy[105].

Kaposi's sarcoma (KS) is a rare, viral-induced malignancy that shows a disproportionately higher risk in organ transplant recipients compared with the general population[106]. Since VEGF is a key player in KS, this angio-proliferative disease probably provides mTOR inhibitors with a special opportunity to exhibit their antitumoral effects. The first report of posttransplant KS regression after switching from CsA to SRL in two kidney transplant recipients was described by our group[107] and was subsequently confirmed by Stallone, at al.[108] in 15 kidney transplant recipients after a switch from an immunosuppressive regimen based on CsA and MMF to a regimen based on SRL.

Management of immunosuppressive therapy in patients with posttransplant cancer

Preventing posttransplant de novo *malignancy*

The clinical results of different immunosuppressive regimens available to date suggest that immunosuppressive therapies that contain mTOR inhibitors have a lower *de novo* malignancy risk, and that this risk is even lower if the regimen does not contain CNI[102,103,105,109]. The final decision in

a patient should be weighed up mainly with the immunologic risk and, obviously, with the various spectrums of other pharmacologic secondary effects. Patients with exceptionally high risk for developing malignancy related morbidity and/or mortality (history of several NMSC[102,105], second transplantation with a history of PTLD and especially of KS[110-113], liver transplantation for hepatocellular carcinoma in patients with cirrhosis[27,114], and history of pretransplant tumor[115]) could benefit from immunosuppression with low malignancy risk. Several studies have reported reduced overall rates of any posttransplant *de novo* malignancy and non-skin solid malignancy with mTOR inhibitor therapy[102-104]. This evidence supports the preferential use of mTOR inhibitor-based regimens in the management of these patients.

Immunosuppressive therapy management in recipients with de novo malignancies

Currently, the only strongly recommended measure is reduction of immunosuppression in organ transplant recipients with *de novo* KS or NHL, and the benefit/risk balance of this measure is more debated for other solid tumors. Although the efficacy of reduction or even cessation of immunosuppression in KS or NHL has been clearly established[112,116], this approach could be associated with a significant risk of acute rejection or graft loss[117], and KS frequently recurs when immunosuppressive therapy is reintroduced or a second transplantation is performed[118]. Alternative strategies based on mTOR-inhibitor conversion and withdrawal of other immunosuppressive drugs, especially CNI, could achieve a balance between adequate levels of immunosuppression to protect the allograft, and a potentially anti-oncogenic effect. The efficacy of SRL conversion and CNI withdrawal in posttransplant cutaneous KS has been strongly established[107-109,120]. However, clinical data on visceral and severe forms of KS are scarce, especially if a long delay before its introduction and the extension and severity of the KS lesions are responsible for the relapses[120].

Non-melanoma skin cancer is often easily resolved with surgical treatment. However, some patients have multiple skin cancers, and others suffer from cancers with a high risk of metastasis and even death[19,39,121-127]. In these patients, reduction of immunosuppression is a useful adjuvant strategy[128]. An international expert consensus for the reduction of immunosuppression for transplant-associated skin cancer has recently been published[129]. This exceptionally valuable publication has developed consensus on the level of tumor burden or metastatic risk of skin cancer warranting consideration of reduction of immunosuppression, and on the risks associated with reduction of immunosuppression in multiple or high-risk skin cancers. However, this consensus does not address another reasonable strategy, i.e. conversion from a CNI-based immunosuppressant regimen to one based on mTOR inhibitors[130]. In our opinion, despite the lack of direct evidence, there is enough data supporting a decreased risk of *de novo* NMSC with mTOR inhibitors, compared with other immunosuppressive regimens, to recommend this alternative[102,105].

Conventional oncologic treatment is the cornerstone of posttransplant solid-tumor management. However, evidence of faster and more aggressive progression of solid tumors under immunosuppressive therapy has already been discussed. These data reaffirm the appropriateness of reducing immunosuppression in organ transplant recipients after the development of a solid tumor. In our opinion, a significant reduction of immunosuppression can be strongly recommended. This could improve response to appropriate oncologic treatment for the specific tumor type. Importantly, experimental data from Kohel, et al.[85] support the clinical experience of many physicians that patients with solid cancers are able to undergo strong reductions in immunosuppressive therapy for long periods without signs of rejection.

Experimental evidence of the efficacy of mTOR inhibitors in reducing tumor growth and metastasis should also be considered. The mTOR

inhibitors by themselves may have a positive impact on patient prognosis. In addition, they allow safer withdrawal of other immunosuppressive drugs with a demonstrated pro-oncogenic effect, especially CNI. Finally, mTOR inhibitors seem to show a synergic action with other antineoplastic agents[130]. Taken together, these findings support the use of mTOR inhibitors as an adjuvant in the treatment of posttransplant solid tumors. However, the appropriate indication of mTOR inhibitors should probably await the clinical trials currently in development about the efficacy of this pharmacologic group in different tumor types. Finally, the use of mTOR inhibitors as antitumor agents in transplant recipients, especially renal transplant recipients, would be limited by the presence of a significant degree of proteinuria or severe deterioration of renal function[131].

Acknowledgments

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