Risk factors associated with post–kidney transplant malignancies: an article from the Cancer-Kidney International Network

Ben Sprangers1,2,3, Vinay Nair4, Vincent Launay-Vacher3,5, Leonardo V. Riella6 and Kenar D. Jhaveri3,4

1Department of Microbiology and Immunology, KU Leuven and Division of Nephrology, University Hospitals Leuven, Leuven, Belgium, 2Department of Microbiology and Immunology, KU Leuven and Laboratory of Experimental Transplantation, University Hospitals Leuven, Leuven, Belgium, 3Cancer-Kidney International Network, Brussels, Belgium, 4Department of Medicine, Division of Kidney Diseases and Hypertension, Hofstra Northwell School of Medicine, Hempstead, NY, USA, 5Service ICAR and Department of Nephrology, Pitié-Salpêtrière University Hospital, Paris, France and 6Department of Medicine, Schuster Transplantation Research Center, Renal Division, Brigham and Women’s Hospital, Boston, MA, USA

Correspondence and offprint requests to: Ben Sprangers; E-mail: ben.sprangers@uzleuven.be

Abstract

In kidney transplant recipients, cancer is one of the leading causes of death with a functioning graft beyond the first year of kidney transplantation, and malignancies account for 8–10% of all deaths in the USA (2.6 deaths/1000 patient-years) and exceed 30% of deaths in Australia (5/1000 patient-years) in kidney transplant recipients. Patient-, transplant- and medication-related factors contribute to the increased cancer risk following kidney transplantation. While it is well established that the overall immunosuppressive dose is associated with an increased risk for cancer following transplantation, the contributive effect of different immunosuppressive agents is not well established. In this review we will discuss the different risk factors for malignancies after kidney transplantation.

Key words: immunosuppression, kidney transplantation, malignancy, risk factor

Introduction

Malignancy is one of the most common causes of death in kidney transplant recipients [1, 2]. In kidney transplant recipients, the incidence of cancer is generally increased 2- to 3-fold compared with the general population [3, 4]. This increased cancer risk is not spread evenly over all types of cancers; while some cancer incidences are not increased (breast, prostate, ovarian, brain and cervical cancer), others are increased substantially (lung, colon, liver, lymphoma, melanoma and non-melanoma skin cancer). Cancer-related mortality rates are also higher in kidney transplant recipients compared with the general population [5].

Patient-, transplant- and medication-related factors contribute to the increased cancer risk following kidney transplantation. Immunosuppression is considered the most important...
Epidemiology and clinical presentation

Analyses from different registry data estimate the general increase in cancer incidence in kidney transplant recipients to be two- to three-fold compared with the general population [3, 4, 16–25]. Estimates of cancer incidence obtained from different registries differ widely, suggesting that data quality is problematic. This was confirmed in a recent study by Yanik et al. [26], who compared cancer diagnoses collected in the Scientific Registry of Transplant Recipients (SRTR) database with 15 linked cancer registries for colorectal, liver, lung, breast, prostate and kidney cancers, melanoma and non-Hodgkin lymphoma (NHL). They concluded that SRTR cancer data were strikingly incomplete, as only 36.8% of cancers were both registered in the SRTR database and cancer registries, whereas 47.5% of cancers were only documented in cancer registries and 15.7% were only documented in the SRTR database [26]. The estimated sensitivity for identifying cancer was only 52.5% for the SRTR and 84.3% for cancer registries [26].

Data from the USA concerning 175 732 solid organ transplant recipients (58.4% kidney transplant recipients) during the period 1987–2008 showed that the standardized incidence ratio (SIR) for cancer overall was 2.1 (95% CI 2.06–2.14) higher compared with the general population, with an excess absolute risk of 719 cases per 100 000 person-years [3]. The majority of these patients included in these studies were kidney transplant recipients, whereas 47.5% of cancers were only documented in cancer registries and 15.7% were only documented in the SRTR database [26].

Pathogenesis and transplant-specific risk factors

Several factors have been linked to the increased incidence of malignancies among transplant recipients [6], including age, sex, sun exposure, previous cancer, concomitant viral infection, cumulative dose of immunosuppression, type of immunosuppression, AR and the duration of pre-transplant dialysis (Table 1 and Figure 1) [38, 39]. Risk factors for patient death from cancer include male gender, a history of prior cancer and immunosuppression and lymphocyte-depleting antibodies [5].

Donor transmission

A variety of donor-transmitted malignancies have been documented, including melanoma and cancers of the lung, breast, colon, rectum and kidney, Kaposi sarcoma and glioblastoma multiforme. Donor transmission as a cause of post-transplant malignancy is a rare but dreaded event, as it might result in metastatic disease in the transplant recipient [40–47]. Reported transmission rates are <0.03%, but these are likely under-reported and underdiagnosed [41, 48, 49]. The most common transmitted cancer types are renal cancer, lung cancer, melanoma and lymphoma [46, 50, 51]. The risk of donor transmission depends on the type and extent of the original donor cancer. A donor history of melanoma, lung carcinoma or chorio-carcinoma seems to be associated with high transmission risk and death and organs from such donors should not be accepted.
for transplantation [46]. In contrast, organs from donors with renal cell cancer without capsular invasion and central nervous system tumours (except medulloblastoma) are acceptable, as the risk seems to be low, reflecting the limited metastatic potential of these tumours [46, 52]. Regarding outcome, early donor-transmitted cancer (diagnosed <6 weeks of transplantation) was associated with a better outcome compared with late donor-transmitted cancer [51]; 5-year survival was 83% for kidney recipients with donor-transmitted cancer compared with 93% for recipients without donor-transmitted cancer (P = 0.077) [50, 51]. Recipients with transmitted renal cancers had the best outcomes, with >70% 2-year survival post-transplantation [50], while patients with melanoma and lung cancers had <50% 2-year survival post-transplantation [50].

Donor type

Differences in the type of transplant (living versus deceased) have been associated with cancer risk. In a study by Ma et al. [53], the overall risks for cancer were 1080, 1444 and 2018 per 100 000 patient-years for recipients of living donor, standard and expanded criteria deceased donor kidney recipients, respectively. This increased risk with different donor types was independent of age, sex, and time on dialysis [53]. Recipients of living-donor kidneys had a lower risk of cancer, particularly for genitourinary cancer and PTLD [53].

Recipient age and time on dialysis

Both in paediatric and adult kidney transplant recipients, recipient age has been identified as an independent risk factor of post-kidney transplant malignancies [54, 55]. With increasing recipient age, this is an important factor in the overall increasing incidence of post-transplant cancer in kidney transplant recipients. Time on dialysis before transplantation has also been identified as a risk factor for developing post-transplant malignancy. In a study based on the ANZDATA database, Wong et al. [38] reported a linear relationship between the duration of dialysis and the risk of solid organ cancer after transplantation, irrespective of recipient age. In a very interesting article, Yanik et al. [56] evaluated the incidence of cancer types depending on non-renal function interval (time on dialysis either on wait list or after transplant failure) or kidney function interval (time with a functioning graft and thus on immunosuppression), applying a linkage between the SRTR and several US cancer registries. While the incidence of infection-related and immune-related cancer (Kaposi sarcoma, NHL, lip cancer and non-epithelial skin cancer) was higher during kidney function intervals, end-stage renal disease (ESRD)-related cancer incidence (kidney cancer and thyroid cancer) was lower during kidney function intervals. Every change of status (non-renal function interval/kidney function interval) was associated with a changing incidence for NHL, melanoma, lung, pancreatic and non-epithelial skin cancers (higher during function intervals) and kidney and thyroid cancers (higher during non-function intervals), suggesting potent short-term effects of kidney dysfunction and immunosuppression on cancer incidence [56].

Previous cancer

A history of cancer prior to kidney transplantation in the recipient increases the risk of death by 30% [57]. These findings were also confirmed in another study showing that kidney transplant recipients with a pre-transplant cancer are 3.7 times more likely to die of cancer post-transplantation [5]. Acuna et al. [58] performed an interesting meta-analysis including 32 cohort studies on solid organ transplant recipients with a pre-transplant malignancy in remission. They demonstrated that pre-transplant malignancy is associated with an increased risk of all-cause mortality (pooled hazard ratio 1.51), cancer-specific mortality (pooled hazard ratio 3.13) and of developing de novo malignancies (pooled hazard ratio 1.92) after transplantation compared with solid organ transplant recipients without a pre-transplant malignancy [58]. These studies clearly identify kidney transplant recipients with pre-transplant cancer as a high-risk

![Fig. 1. Cancerogenesis following kidney transplantation (adapted from Riella [37]).](image-url)

### Table 1. Risk factor for post-transplant malignancies

| Risk factor for post-transplant malignancies | Patient-related risk factors | Transplant-related risk factors | Medication-related risk factors |
|---------------------------------------------|-----------------------------|-------------------------------|--------------------------------|
|                                             | Recipient age               | Donor transmission            | Net immunosuppression          |
|                                             | Previous cancer             | Donor type                    | Induction therapy              |
|                                             | Sun exposure                 | Rejection                     | Maintenance therapy           |
|                                             | Viral infection              |                               |                                |
|                                             | Duration of dialysis         |                               |                                |
|                                             |                               |                               |                                |
|                                             |                               |                               |                                |

Risk factors for post-transplant malignancies

- **Recipient age**
- **Previous cancer**
- **Sun exposure**
- **Viral infection**
- **Duration of dialysis**
- **Donor transmission**
- **Donor type**
- **Rejection**
- **Net immunosuppression**
- **Induction therapy**
- **Maintenance therapy**
patient population requiring tailored screening and management strategies.

Organ predilection

The incidence of specific malignancies varies according to the transplanted organ [3]. While in some types of transplantation (lung and liver), post-transplant malignancies tend to occur in the transplanted organ, in kidney transplantation this does not appear to be the case (kidney cancer in kidney transplant recipients primarily affects the native kidney) [3, 4, 16–23]. In addition, other cancer types vary depending on the transplanted organ. For example, the risk of NHL in lung transplant recipients is doubled compared with kidney, heart or liver transplant [3]. It is well established that kidney cancer is greatly increased in dialysis patients and kidney transplant recipients [3, 4, 16–23]. Prolonged time on dialysis has been identified as a risk factor for the development of kidney cancer [59, 60] and the incidence of kidney cancer can be as high as 100 times the expected incidence [61, 62]. While kidney cancer in native kidneys is frequent, cancer in the transplanted kidney is rare. In a European retrospective study, 20 patients were identified with kidney cancer in the transplanted kidney: 85% were papillary renal cell carcinoma (RCC) and 15% were clear cell RCC [63]. The tumours were small at the time of diagnosis and all patients were managed with ablation therapy (cryoablation or radiofrequency ablation) without a reduction or change in their immunosuppressive therapy [63].

Sun exposure

In the development of skin cancer, sun exposure is an established risk factor [64–66]. The application of sun block and administration of nicotinamide have both been demonstrated to reduce the incidence of non-melanoma skin cancer [67–70].

Viral infection

At least four viruses are believed to be co-carcinogenic in transplanted patients: EBV (Hodgkin’s and NHL), human herpesvirus 8 (HHV8; Kaposi sarcoma) [71–73], human papillomavirus (HPV; cervix, vulva, vagina, anus and some oro-pharynx cancers) and Merkel cell polyomavirus (Merkel cell skin carcinoma). EBV has conclusively been implicated in the pathogenesis of PTLD following kidney transplantation [74, 75] and EBV status is one of the most important risk factors for PTLD. More than 50% of PTLD cases are EBV related, and EBV mismatch between donor and recipient (an EBV-negative receptor engrafted with an EBV-positive donor) is associated with a 20-fold increased risk for PTLD [76–78]. Moreover, primary EBV infection post-transplant is a major risk factor for EBV-positive PTLD in early onset PTLD [15]. Additionally, other viruses have been associated with the development of cancer, e.g. hepatitis B and C (HBV and HCV; liver cancer) and BK polyomavirus (urological cancers) [79–87]. The central role of the immune system in the control of oncogenic viruses was emphasized by the findings of Grulich et al. [4], where a similar increase of virus-associated cancers was observed in solid organ transplant patients and patients with HIV/AIDS. As far as cytomegalovirus (CMV) and post-transplant malignancy are concerned, conflicting results have been reported [88–92], so at this time it is not clear whether CMV infection is associated with an increased risk of post-transplant cancer. A recent study demonstrated that cancer risk after kidney transplantation during childhood is particularly increased for virus-related cancers [54].

Rejection and treatment

As the total dose of immunosuppression is related to the risk of post-transplant malignancy, it is no surprise that rejection episodes and anti-rejection therapy are associated with the risk of post-transplant malignancy, as doses of maintenance immunosuppression including calcineurin inhibitors, antimetabolite and/or corticosteroids are often increased during the treatment of rejection, thereby contributing to increased T cell dysfunction [93]. Besides T cell dysfunction, systemic inflammation and concomitant release of cytokines and chemokines may promote malignant transformation [94, 95]. In the CTS, anti-rejection therapy with OKT3 or anti-thymocyte globulin (ATG) increased the overall cancer risk [96]. In a recent analysis of the ANZDATA, Lim et al. [29] studied the risk of incident cancer among kidney transplant recipients who have experienced AR, stratified by the use of T cell–depleting antibodies. The study included 7153 kidney transplant recipients transplanted between 1997 and 2009, of which 6.5% developed cancers. The risk for cancer after first kidney transplantation was significantly higher in patients experiencing AR treated with T cell–depleting antibodies (adjusted hazard ratio 1.42) compared with kidney transplant recipients not experiencing AR and the excess cancer risk was mainly confined to genitourinary tract cancers [29]. Also, treatment of rejection with high-dose steroids can adversely affect the risk for PTLD [97].

Maintenance immunosuppression

Maintenance immunosuppression is essential after kidney transplantation to prevent allograft rejection. Although it is accepted that overall immunosuppression dose is associated with an increased cancer risk following transplantation, the contributive effect of different immunosuppressive agents is not established. The mechanisms linking immunosuppression dose to the increased incidence of cancer are numerous and include decreased immune surveillance of tumours, decreased antiviral responses resulting in a specific increase of virus-induced tumours and possibly the direct carcinogenic effect of immunosuppressive drugs such as cyclosporine and azathioprine (Table 2) [6].

The cumulative immunosuppressive dose (net immunosuppressive dose for the entire life) is associated with the risk for cancer post-transplant. For example, patients previously treated with immunosuppression for primary glomerular disease [128] or for AR [29] are at higher risk to develop cancer. Hibberd et al. [128] reported an association between pre-transplantation immunosuppression and increased risk for four cancer groups: anogenital cancer, NHL, breast cancer and urinary tract cancer (excluding kidney). Grulich et al. [4] analyzed seven studies of people with HIV/AIDS (n = 444 172) and five of transplant recipients (n = 31 977) for 20 of the 28 types of cancers. A significantly increased cancer incidence was found in both populations, and most cancers that occurred at increased rates involved oncogenic viruses (e.g. EBV, HHV8, HPV, HBV and HCV). The rates of most common epithelial cancers (breast or prostate cancer) were not increased [4]. The similarity of the pattern of increased risk of cancer in the two populations suggests that it is immune deficiency rather than other risk factors for cancer that is responsible for the increased risk. Of note, there were also some discrepancies noted, as some cancer types (thyroid, kidney, melanoma and bladder cancers) were increased in the transplant population but not in the HIV/AIDS cohorts.

Although results suggest that currently available immunosuppressive agents influence different anticancer pathways
Table 2. Immunosuppressive drugs and oncogenesis

| Immunosuppressant agent | Method of action | Role in carcinogenesis |
|-------------------------|------------------|------------------------|
| Calcineurin inhibitor   | Inhibition of IL-2 production through binding and inhibition of cyclophilin (cyclosporine) and FKBP-12 (tacrolimus), respectively | Production of TGF-β [98, 99] | Production of VEGF [98, 100] | Production of interleukin-6 (IL-6) (promotion of EBV-induced B-cell growth) [101] | Promotion of invasive behaviour of non-transformed cells [98] | Reduced ability to repair radiation-induced DNA damage | Enhanced apoptotic effects of taxol and IFN-γ on human gastric and bladder cancer cells [102, 103] | Increased rate of lymphoproliferative disorders in HSV-infected mice [104] | Intercalation at the DNA level, inhibiting repair splicing and eliciting codon misreads [105] |
| Azathiopurine            | Inhibition of DNA and RNA synthesis through incorporation of thiopurine analogues | Anti-proliferative effect on leukaemia and solid tumour | Inhibition of adhesion molecules [107, 108–114] | Suppressed glycosylation and expression of several adhesion molecules [109, 115] | Inhibition of adhesion of colon adenocarcinoma cells to endothelial cells [116] |
| Mycophenolate mofetil   | Inhibition of inosine monophosphate dehydrogenase and de novo purine biosynthesis | Inhibition of interleukin-10: decreasing tumour cell JAK/STATs activity [120] | Decreased VEGF-A and VEGF-C signalling, impaired tumour angiogenesis [101, 119, 122, 123] | Inhibition of growth signals in PTLD-associated EBV + B-cell lymphomas [124] | Inhibition of replication of EBV-positive B cells, T cells and NK cells [125, 126] | Inhibition of ultraviolet B–induced metalloproteinase activation [127] |
| mTOR inhibitors         | Inhibition of mTOR pathway | Increased development of microsatellite DNA instability [106] | Direct antitumour effect by inhibition of mTOR pathway [117, 118] | Inhibition of angiogenesis | Inhibition of p70 S6K: decreasing cancer cell proliferation [119, 120] | Inhibition of interleukin-10: decreasing tumour cell JAK/STATs activity [120] | Inhibition of cyclins: blocking cell-cycle activity [121] | Increased rate of lymfoproliferative disorders in HSV-infected mice [104] | Decreased VEGF-A and VEGF-C signalling, impaired tumour angiogenesis [101, 119, 122, 123] | Inhibition of growth signals in PTLD-associated EBV + B-cell lymphomas [124] | Inhibition of replication of EBV-positive B cells, T cells and NK cells [125, 126] | Inhibition of ultraviolet B–induced metalloproteinase activation [127] |

[101], it is not clear whether currently used medications such as cyclosporine, tacrolimus, azathioprine or mycophenolate are associated with different cancer risks [14, 129–131]. mTOR inhibitors have been reported to have less cancer risk compared with alternative immunosuppressive therapies [132]; however, in a recent systematic review, decreased cancer incidence in kidney transplant recipients treated with mTOR inhibitors did not result in improved overall survival [133]. As induction therapy is concerned, interleukin-2 (IL-2) receptor antagonist (IL-2Ra) induction does not appear to be associated with an increase in cancer [39], whereas some studies find a small increase in cancer and cancer death with lymphocyte-depleting antibodies [5, 134, 135]. Moreover, there appear to be differences in the different types of lymphocyte-depleting antibodies.

Induction therapy
Multiple agents have been used as induction therapy at the time of kidney transplantation (e.g. OKT3/muromonab, polyclonal lymphocyte-depleting antibodies, anti–IL-2 receptor (CD25) antibodies and alemtuzumab (anti–CD52). As both CD4+ and CD8+ T cells are crucial in adaptive antiviral immunity, depletion of both populations of T cells with T cell–depleting antibodies would increase the susceptibility of individuals to a higher risk of virus-associated diseases [136]. Direct antitumour effects have also been attributed to CD4+ T helper 1 cells, CD8+ cytotoxic T cells and natural killer (NK) cells [137]. Polyclonal T cell–depleting antibodies target a variety of T and NK cell-derived antigens, including CD2, CD3, CD4, CD8 and CD16, but also markers expressed by leucocytes, B cells and plasma cells, which may explain the predisposition to infections and cancer complications associated with the use of these agents [138–140].

The immunosuppressive potency of OKT3 is greater than that of polyclonal lymphocyte–depleting agents and the use of OKT3 has clearly been associated with an increase in lymphoma risk [14, 141–143]. OKT3 is no longer commercially available, but other forms of induction therapy are still currently in use and from the late 1990s onwards, rabbit ATG (rATG) became the most commonly used polyclonal agent in the USA [144, 145], and later worldwide [146, 107].

Polyclonal induction therapy: When evaluating the cancer-inducing effect of different types of polyclonal lymphocyte-depleting agents, the data are limited and hard to interpret. Available registry analyses have often combined all polyclonal lymphocyte-depleting agents into one category and often span multiple decades. Combining different types of induction agents (e.g. polyclonal induction agents or ATG) is problematic, as there are clear differences in the risk of PTLD associated with different preparations [141, 147]. Furthermore, over time the type of lymphocyte-depleting agent, the average dose of rATG and the type and dose of concomitant immunosuppressive agents have changed significantly. During the 1980s and early 1990s, OKT3 and non-rATG preparations were most widely used [144, 145], and this was associated with a marked increase in the incidence of PTLD [148, 149]. From the late 1990s onwards, rATG became the most commonly used polyclonal agent in the USA [144, 145], and later worldwide [146, 107]. Finally, in the 1980s rATG dosing was markedly higher than it is now (e.g. total dose...
14 mg/kg versus 6 mg/kg now) [150] and it has been demonstrated that higher rATG dosing is associated with a higher risk of PTLD [13].

Earlier studies have suggested an association of induction therapy with T cell–depleting antibodies with an increased risk of PTLD. In an analysis of the CTS, the SIR of lymphoma compared with a similar non-transplant population was higher with T cell–depleting antibody induction as compared with IL-2Ra or no induction therapy [143]. Also, a study of the SRTR and the United States Renal Data System databases reported similar results (70% increased risk of PTLD in renal transplant recipients receiving monoclonal and/or polyclonal T cell–depleting antibodies as induction therapy) [10, 14]. Also, an earlier analysis of the ANZDATA registry demonstrated that the use of T cell–depleting antibodies (as induction or as treatment for rejection) was associated with a more than two-fold increased risk of early onset NHL after transplantation [9]. Registry database studies reported results regarding rATG use and the occurrence of PTLD have been mixed. Only three studies looked at rATG specifically and two found an increased risk for PTLD while one did not [10, 11, 151]. Other registry studies of PTLD risk have grouped multiple lymphocyte-depleting induction agents together for the purpose of analysis, in some cases including OKT3 [44, 152–155]. Three prospective randomized trials followed patients up to 5 years after kidney transplantation [156–158]. The incidence of PTLD and the follow-up time were too limited to allow for meaningful conclusions [159–162]. Finally, a systematic review by Marks et al. [13] evaluated the rate of PTLD in recipients of kidney or heart allografts and pointed to the importance of antiviral prophylaxis, as in this study; the absence of antiviral prophylaxis was the greatest risk factor for the development of PTLD rather than the use of induction therapy.

IL-2R antagonist induction: In the CTS, induction therapy with polyclonal and IL-2Ra induction was not associated with significant increases in the risk of PTLD when compared with no induction therapy [14]. However, universal use of IL-2Ra induction is increasingly questioned, as it does not provide benefit in low-risk kidney transplant recipients compared with no induction therapy, while being inferior compared with ATG in high-risk kidney transplant recipients [161, 163–165]. In a recent observation study, rATG was associated with a decreased risk of adverse outcomes (including mortality) compared with alemtuzumab and basiliximab as induction therapy [166].

Alemtuzumab: In the Transplant Cancer Match study, the use of alemtuzumab as induction therapy was associated with a 79% increase in NHL, a 2.5-fold increase in colorectal cancer and a 3-fold increase in thyroid cancer after transplantation [142]. Other studies have reported mixed results regarding the use of alemtuzumab and PTLD; although one study did not find an association [11], another using a more recent Organ Procurement and Transplantation Network cohort did [78]. A recent study in small bowel allograft recipients receiving alemtuzumab demonstrated earlier onset of lymphoplasmacytic hyperplasia, the most indolent form of B lymphocyte clonal expansion, compared with patients receiving the IL-2Ra induction agent daclizumab [167].

Maintenance therapy
Calcineurin inhibitors: In kidney transplant recipients, both cyclosporine and tacrolimus are associated with an increased risk of malignancy [101]. In a French prospective randomized study involving 231 renal allograft recipients, low-dose (75–125 ng/mL) cyclosporine was associated with a lower incidence of secondary cancers (particularly skin cancers) compared with normal-dose (150–250 ng/mL) cyclosporine at a median of 66 months follow-up [168]. Some evidence suggested a higher risk for PTLD under tacrolimus versus cyclosporine [169, 170]. However, subsequent analyses by the same group postulated that this was the result of a lack of experience with the agent and overaggressive dosing at the time of introduction of tacrolimus in clinical practice. Ultimately, reduced tacrolimus trough levels led to substantial declines in the risk of PTLD [171]. An analysis of the CTS demonstrated that cyclosporine did not confer added risk for the development of NHL compared with azathioprine/steroid treatment, whereas treatment with FK506 increased the risk approximately 2-fold [96].

Azathioprine: The use of azathioprine has long been recognized as an as an etiologic factor in the development of neoplasia, especially in the development of late non-melanoma skin malignancies (particularly squamous cell cancer) [23, 101, 172, 173]. Furthermore, azathioprine is associated with the development of myelodysplastic syndrome [108].

Mycophenolate mofetil: Some patient studies have suggested that the risk of developing malignancies is decreased with the use of mycophenolate mofetil [107, 174, 175], while other studies could not demonstrate a reduction in cancer incidence with mycophenolate- versus non-mycophenolate-based therapy [174]. An SRTR analysis reported that the introduction of mycophenolate mofetil was associated with the greatest decrease in relative risk for the development of PTLD [4]. When patient outcomes during different eras of immunosuppression were compared, the use of MMF was also found to be associated with a reduction in the incidence of PTLD [9, 174, 176]. In patients, the principal anti-tumour mechanism associated with mycophenolate mofetil use may be due to the decreased incidence of AR.

mTOR inhibitors: While for most classes of immunosuppressive agents there is a dose-dependent relationship between the dosage of the immunosuppressive agent and secondary malignancies, this does not hold true for mTOR inhibitors such as sirolimus and everolimus. In humans, evidence suggests that sirolimus may confer a decreased risk of malignancy compared with other immunosuppressive medications [101, 133, 177–181]. Case reports and case series have reported that in renal transplant recipients with Kaposi sarcoma, switching from cyclosporine to sirolimus resulted in total resolution of the Kaposi sarcoma [179, 182, 183]. In the TUMORAPA study, where patients with a history of squamous cell carcinoma were studied, conversion to sirolimus significantly reduced the risk for relapse when compared with those who were maintained on calcineurin inhibitor-based therapy [184]. For non-melanoma skin cancer, Campbell et al. [185] reported that conversion to sirolimus after 1-year post-transplant resulted in a lower yearly incidence rate of non-melanoma skin cancer and also a lower incidence of new or recurrent non-melanoma skin cancer. Individual studies regarding the incidence of cancer associated with the use of sirolimus have been conflicting [177, 186–193]. In a study linking the US SRTR database with 15 population-based cancer registries and national pharmacy claims, cancer incidence in 32 604 sirolimus-exposed and sirolimus non-exposed kidney transplant recipients was studied. The incidence of prostate cancer was higher during sirolimus use (hazard ratio 1.86), while the incidence of other cancers was similar or lower, with a 26% decrease in overall cancer incidence excluding prostate carcinoma (hazard ratio 0.74). The authors postulate that the increase in prostate cancer diagnosis is due to sirolimus, effects on screen detection. In addition, two meta-analyses have been
published demonstrating a lower overall cancer incidence with the use of sirolimus [133, 194]. In the meta-analysis of Knoll et al. [133], including 21 randomized controlled trials with patient-level data from 5876 patients, it was demonstrated that sirolimus was associated with a 40% reduction in malignancy risk and a 56% reduction in the risk of non-melanoma skin cancer (0.44, 0.30 to 0.63) compared with controls. This effect is restricted to patients converting to sirolimus from another immunosuppressive regimen, as analysis of de novo sirolimus trials revealed no difference in malignancy risk between sirolimus and controls [133]. Moreover, in a study analyzing Medicare claims data for transplant recipients, de novo use of sirolimus was associated with a 22% increased risk of PTLD [195]. Remarkably, in the meta-analysis of Knoll et al. [133], the decreased risk of cancer development was associated with an increased overall mortality risk due to cardiovascular and infection-related deaths. The authors speculate that increased sirolimus-induced cardiovascular risk factors (anaemia, proteinuria, hyperglycaemia and hyperlipidaemia) and overimmunosuppression with sirolimus might have contributed to these findings [133]. Based on these studies, universal sirolimus use in kidney transplant recipients cannot be recommended at this time.

Belatacept: For the co-stimulation blocker belatacept, an inhibitor of T cell proliferation, PTLD risk appears similar to that seen under calcineurin inhibitor therapy [196], however, belatacept is contraindicated in EBV-seronegative recipients. Although initially a number of PTLDs of the central nervous system were reported in patients treated with belatacept [197, 198], follow-up data of both the BENEFIT study and, more recently, a Phase 2 study where low immunologic risk patients were switched from calcineurin inhibitor therapy to belatacept showed a mild albeit small increase in post-transplant malignancies [199–202].

### Screening

Since cancer before transplantation increases the risk of post-transplant malignancy, guidelines have been developed outlining waiting times for different types and stages of cancer (Table 3). A systematic review by Batabyal et al. [207] concluded that none of the available recommendations are backed by strong evidence. We recommend seeking an expert oncologist’s opinion regarding cancer-free survival, patient life expectancies and optimal cancer surveillance. Clinicians have to realize that even longer waiting times do not eliminate the risk for cancer recurrence and cancer-related death [57]. In a Swedish population-based cohort of solid organ transplant recipients, the increased rate of death was greatest for patients with waiting times of ≤5 years but persisted with waiting times of >10 years among recipients with prior aggressive cancer types (gastrointestinal, breast, kidney/urothelial and hematologic malignancies) [57].

The optimal cancer screening strategy to detect post-transplant cancers in an early stage is not defined (Table 4). In general, many experts recommend using general practice guidelines in kidney transplant recipients [208–215]. Several centres routinely screen for native kidney cancer, as the risk for kidney cancer is greatly increased in both the dialysis and kidney transplant populations [3, 4, 16–23, 216, 217]. In a medical decision analysis, screening for kidney cancer in all transplant recipients would have a small benefit at relatively high cost [218]. However, directed screening using ultrasound in those with documented acquired cystic kidney disease or those with a previous cancer in a contralateral kidney might be cost effective. Modelling studies by Wong et al. [219, 220] suggest that screening for colon and cervical cancer would be cost effective in the kidney transplant population. In a population-based cohort of Ontario between 1997 and 2010, 77.5, 69.8 and 91.4% of eligible solid organ transplant recipients were not up to date with colorectal, cervical and breast cancer screening, respectively [221].

### Treatment of post-transplant cancer

In general, a reduction in immunosuppression is recommended or kidney transplant recipients upon cancer diagnosis. In the above-mentioned study of Yanik et al. [56], it was noted that the incidence of infection-related cancers was higher and the incidence of ESRD-related cancers was lower during kidney function intervals (time on immunosuppression), suggesting that a reduction of immunosuppression affects different cancer types differently. Similar findings were reported by van Leeuwen et al. [222], who performed a population-based retrospective cohort study and compared the cancer incidence in kidney transplant recipients during periods of transplant function (and immunosuppression) and after transplant failure (when immunosuppression is
The SIRs for NHL, lip cancer and melanoma were significantly elevated during periods of transplant function. For leukaemia and lung carcinoma, SIRs remained elevated after transplant failure, while the SIRs for kidney/urinary tract and thyroid cancers significantly increased after transplant failure. These data suggest that while the effect of immunosuppression on cancer risk is rapidly reversible for some cancers (mainly infectious-related cancers), this does not hold true for other cancer types (ESRD-related cancers) [222]. Some centres convert patients with non-melanoma skin cancer to mTOR therapy, as randomized clinical trials have shown fewer skin cancers in mTOR-treated patients [184, 185]. Also, for other solid and hematologic cancers, mTOR inhibitors have had marginal success [223, 224]. However, routine conversion to mTOR inhibitors to improve outcomes in all cancers or to prevent long-term cancer development in all solid organ transplant recipients is not widely practiced at this time, as data are lacking to support this practice.

Outcome

Data suggest that cancer as a cause of death is on the rise. For example, in Australia and New Zealand, cardiovascular deaths are decreasing while cancer mortality is increasing [1]. Malignancy accounts for 8–10% of all deaths in the USA (2.6 deaths/1000 patient-years) and >30% of deaths in Australia (5/1000 patient-years) [1, 2]. The data regarding standardized mortality rates (SMRs) have been conflicting. While some studies have suggested that the cancer-related SMR has increased with the same magnitude as the SIR in transplant recipients [224], other studies have shown a more nuanced picture [5]. In a study from Hong Kong, the cancer SIR and SMR in kidney transplant recipients were very similar (2.9 and 2.3, respectively) [225]; high SMRs were associated with lymphoma, leukaemia, kidney, colon, lung, bladder, melanoma and stomach cancers, while lymphoma, liver, colorectal and lung were associated with excess absolute risk of >25 deaths/100 000 patient-years [225]. In a US registry analysis by Kibert et al. [5], no overall excess mortality was observed in kidney transplant recipients. Cancer SMRs varied substantially with age group; cancer SMRs were 23-fold and 4.4-fold higher in patients <20 years and 20–39 years of age, respectively, while cancer SMRs were lower in patients >60 years of age [5]. The cancer death rates were >500/100 000 patient-years for patients >60 years of age compared with 13/100 000 patient-years for patients 20–39 years of age [5]. So in older patients who are at the highest risk to die from cancer, there is no increased risk to die from cancer in kidney transplant recipients. More specific data are available concerning post-transplant lymphoma. The 1-year survival in cadaveric kidney transplant recipients developing lymphoma was 60% and showed little improvement over the study period, while the 5-year survival was ~40% [30]. Interestingly, in this analysis the time of lymphoma development after transplantation did not influence survival: 5-year survival in kidney transplantation with lymphoma development <90 days post-transplant and >365 days post-transplant was 41.4% and 37.0%, respectively [30]. Post-transplant lymphoma with lymph node involvement had a good prognosis while disseminated disease had a poor prognosis [30].

Conclusion

Malignancy is one of the most common causes of death in kidney transplant recipients. In general, the cancer incidence in...
solid organ transplant recipients is increased 2- to 3-fold compared with the general population [3, 4]. Moreover, cancer-related mortality rates are also higher in solid organ transplant recipients compared with the general population [5]. Several risk factors for post-transplantation cancer development have been identified and immunosuppression is considered the most important risk factor, as it decreases the immunologic control of oncogenic viral infection and immunosurveillance. Currently available immunosuppressive agents influence different anti-cancer pathways and mTOR inhibitors seem to have a favourable profile in this respect. However, the increased mortality associated with mTOR inhibitor use in a recent meta-analysis argues against their universal use in renal allograft recipients or switching to mTOR inhibition in all patients with post-transplant malignancies. Intense collaboration between nephrologists and oncologists is needed in this field to design safer immunosuppressive regimens and define optimal screening and treatment strategies in kidney transplant recipients.

Funding

No funding was involved in the preparation of this Manuscript.

References

1. Pilmore H, Dent H, Chang S et al. Reduction in cardiovascular death after kidney transplantation. Transplantation 2010; 89: 851–857
2. Collins AJ, Foley RN, Chavers B et al. United States Renal Data System 2011 annual data report: atlas of chronic kidney disease & end-stage renal disease in the United States. Am J Kidney Dis 2012; 59: e1–e420
3. Engels EA, Pfeiffer RM, Fraumeni JF Jr et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306: 1891–1901
4. Grulich AE, van Leeuwen MT, Falster MO et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007; 370: 59–67
5. Kiberd BA, Rose C, Gill JS. Cancer mortality in kidney transplantation. Am J Transplant 2009; 9: 1868–1875
6. Stallone G, Infante B, Grandaliano G. Management and prevention of post-transplant malignancies in kidney transplant recipients. Clin Kidney J 2015; 8: 637–644
7. Caillard S, Dharnidharka V, Agodoa L et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005; 80: 1233–1243
8. Hibberd JD, Trevorill PR, Wlodarczyk JH et al. Cancer risk associated with ATG/OKT3 in renal transplantation. Transplant Proc 1999; 31: 1271–1272
9. van Leeuwen MT, Grulich AE, Webster AC et al. Immunosuppression and other risk factors for early and late non-Hodgkin lymphoma after kidney transplantation. Blood 2009; 114: 630–637
10. Bustami RT, Ojo AO, Wolfe RA et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant 2004; 4: 87–93
11. Kirk AD, Cherikh WS, Ring M et al. Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. Am J Transplant 2007; 7: 2619–2625
12. Pedotti P, Cardillo M, Rossini G et al. Incidence of cancer after kidney transplantation: results from the North Italy transplant program. Transplantation 2003; 76: 1448–1451
13. Marks WH, Ilsley JN, Dharnidharka VR. Posttransplantation lymphoproliferative disorder in kidney and heart transplant recipients receiving thymoglobulin: a systematic review. Transplant Proc 2011; 43: 1395–1404
14. Cherikh WS, Kauffman HM, McBride MA et al. Association of the type of induction immunosuppression with post-transplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. Transplantation 2003; 76: 1289–1293
15. Quinlan SC, Pfeiffer RM, Morton LM et al. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. Am J Hematol 2011; 86: 206–209
16. Collett D, Mumford L, Banner NR et al. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant 2010; 10: 1889–1896
17. Villeneuve PJ, Schaulbe DE, Fenton SS et al. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant 2007; 7: 941–948
18. Webster AC, Craig JC, Simpson JM et al. Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15,183 recipients. Am J Transplant 2007; 7: 2140–2151
19. Adami J, Gabel H, Lindelof B et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2009; 89: 1221–1227
20. Maisonneuve P, Agodoa L, Gellert R et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999; 354: 93–99
21. Kyllo nen I, Salmela K, Pukkala E. Cancer incidence in a kidney-transplanted population. Transpl Int 2000; 13: S394–S398
22. Li WH, Chen YJ, Tseng WC et al. Malignancies after renal transplantation in Taiwan: a nationwide population-based study. Nephrol Dial Transplant 2012; 27: 833–839
23. Kasiske BL, Snyder JJ, Gilbertson DT et al. Cancer after kidney transplantation in the United States. Am J Transplant 2004; 4: 905–913
24. Vajdic CM, van Leeuwen MT, McDonald SP et al. Increased incidence of squamous cell carcinoma of eye after kidney transplantation. J Natl Cancer Inst 2007; 99: 1340–1342
25. Stewart JH, Vajdic CM, van Leeuwen MT et al. The pattern of excess cancer in dialysis and transplantation. Nephrol Dial Transplant 2009; 24: 3225–3231
26. Yanik EI, Nogueira LM, Koch L et al. Comparison of cancer diagnoses between the US solid organ transplant registry and linked central cancer registries. Am J Transplant 2016; 16: 2986–2993
27. Lanza LL, Wang L, Simon TA et al. Epidemiologic critique of literature on post-transplant neoplasms in solid organ transplantation. Clin Transplant 2009; 23: 582–588
28. Stewart T, Tsai SC, Grayson H et al. Incidence of de-novo breast cancer in women chronically immunosuppressed after organ transplantation. Lancet 1995; 346: 796–798
29. Lim WH, Turner RM, Chapman JR, Ma MK et al. Acute rejection, T-cell-depleting antibodies, and cancer after transplantation. Transplantation 2014; 97: 817–825
30. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004; 4: 222–230
72. Montaner S, Sodhi A, Ramsdell AK et al. The Kaposi’s sarcoma-associated herpesvirus G protein-coupled receptor as a therapeutic target for the treatment of Kaposi’s sarcoma. Cancer Res 2006; 66: 168–174

73. Hosseini-Moghaddam SM, Soleimanirahbar A, Mazzulli T et al. Post renal transplantation Kaposi’s sarcoma: a review of its epidemiology, pathogenesis, diagnosis, clinical aspects, and therapy. Transpl Infect Dis 2012; 14: 338–345

74. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer 2004; 4: 757–768

75. Grywalska E, Rolinski J. Epstein-Barr virus-associated lymphomas. Semin Oncol 2015; 42: 291–303

76. Walker RC, Paya CV, Marshall WF et al. Pretransplantation seronegative Epstein-Barr virus status is the primary risk factor for posttransplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. J Heart Lung Transplant 1995; 14: 214–221

77. Sampaio MS, Cho YW, Shah T et al. Impact of Epstein-Barr virus donor and recipient serostatus on the incidence of post-transplant lymphoproliferative disorder in kidney transplant recipients. Nephrol Dial Transplant 2012; 27: 2971–2979

78. Dharmidharka VR, Lamb KE, Gregg JA et al. Associations between EBV serostatus and organ transplant type in PTLD risk: an analysis of the SRTR National Registry Data in the United States. Am J Transplant 2012; 12: 976–983

79. Kenan DJ, Mieczkowski PA, Burger-Calderon R et al. The oncogenic potential of BK-polyomavirus is linked to viral integration into the human genome. J Pathol 2015; 237: 379–389

80. Kenan DJ, Mieczkowski PA, Latulippe E. Polymavirus genomic integration and large T antigen expression: evolving paradigms in human oncogenesis. Am J Transplant 2017; 17: 1674–1680

81. Liu S, Chaudhry MR, Berrebi AA et al. Polymavirus replication and smoking are independent risk factors for bladder cancer after renal transplantation. Transplantation 2017; 101: 1486–1494

82. Papadimitriou JC, Randhawa P, Rinaldo CH et al. BK polyomavirus infection and renourinary tumorigenesis. Am J Transplant 2016; 16: 398–406

83. Oikawa M, Hatakeyama S, Fujita T et al. BK virus-associated urothelial carcinoma of a ureter graft in a renal transplant recipient: a case report. Transplant Proc 2014; 46: 616–619

84. Yan L, Salama ME, Lanciulli C et al. Polymavirus large T antigen is prevalent in urothelial carcinoma post-kidney transplant. Hum Pathol 2016; 48: 122–131

85. Nickeleit V, Singh HK, Goldsmith CS et al. BK virus-associated urinary bladder carcinoma in transplant recipients: productive or nonproductive polymavirus infections in tumor cells? Hum Pathol 2013; 44: 2870–2871

86. Kausman JY, Somers GR, Francis DM et al. Association of renal adenocarcinoma and BK virus nephropathy post transplantation. Pediatr Nephrol 2004; 19: 459–462

87. Emerson LL, Carney HM, Layfield LJ et al. Collecting duct carcinoma arising in association with BK nephropathy post-transplantation in a pediatric patient. A case report with immunohistochemical and in situ hybridization study. Pediatr Transplant 2008; 12: 600–605

88. Couzi L, Levalliant Y, Jamai A et al. Cytochalasin-induced γ6 T cells associate with reduced cancer risk after kidney transplantation. J Am Soc Nephrol 2010; 21: 181–188

89. Courivaud C, Bamoulid J, Gaugler B et al. Cytomegalovirus exposure, immune exhaustion and cancer occurrence in renal transplant recipients. Transpl Int 2012; 25: 948–955

90. Desai R, Collett D, Watson CJ et al. Impact of cytomegalovirus on long-term mortality and cancer risk after organ transplantation. Transplantation 2015; 99: 1989–1994

91. Wong G, Chakera A, Chapman JR et al. Cytomegalovirus and cancer after kidney transplantation: Role of the human leukocyte antigen system? Transpl Infect Dis 2017; 19: 10

92. Verghese PS, Schmeling DO, Knight JA. Valganciclovir administration to kidney donors to reduce the burden of cytomegalovirus and Epstein-Barr virus transmission during transplantation. Transplantation 2015; 99: 1186–1191

93. Halloran FF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004; 351: 2715–2729

94. Iorio N, Vizoso FJ. Inflammation and cancer. World J Gastrointest Surg 2012; 4: 62–72

95. Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. Lancet 1993; 342: 1514–1516

96. Kremers WK, Devabhavi HC, Wiesner RH et al. Post-transplant lymphoproliferative disorders following liver transplantation: incidence, risk factors and survival. Am J Transplant 2006; 6: 1017–1024

97. Hojo M, Morimoto T, Maluccio M et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 1999; 397: 530–534

98. Herman M, Weinstein T, Korzets A et al. Effect of cyclosporin A on DNA repair and cancer incidence in kidney transplant recipients. J Lab Clin Med 2001; 137: 14–20

99. Shihab FS, Bennett WM, Isaac J. Nitric oxide modulates vascular endothelial growth factor and receptors in chronic cyclosporine nephrotoxicity. Kidney Int 2003; 63: 522–533

100. Guba M, Graeb C, Jauch KW. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. Transplantation 2004; 77: 1777–1782

101. Morisaki T, Matsunaga H, Beppu K et al. A combination of cyclosporin-A (CsA) and interferon-gamma (INF-gamma) induces apoptosis in human gastric carcinoma cells. Anticancer Res 2000; 20: 3363–3373

102. Nomura T, Yamamoto H, Mimata H et al. Inflammatory chemokines and metastasis–tracing the accessory. Oncogene 2014; 33: 3217–3224

103. Eiro N, Vizoso FJ. Inflammation and cancer. World J Gastrointest Surg 2012; 4: 62–72

104. Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. Lancet 1993; 342: 1514–1516

105. Swann PF, Waters TR, Moulton DC et al. Inflammatory chemokines and metastasis–tracing the accessory. Oncogene 2014; 33: 3217–3224

106. Offman J, Opelz G, Doehler B et al. Impact of Epstein-Barr virus serostatus on DNA repair and cancer incidence in kidney transplant recipients. J Lab Clin Med 2001; 137: 14–20

107. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. Pediatr Transplant 2004; 7: 777–782

108. Nagai M, Natsumeda Y, Konno Y et al. Enhancement by cyclosporin A of taxol-induced apoptosis of human urinary bladder cancer cells. Urol Res 2002; 30: 102–111

109. Mistrikova J, Mrmusova M, Durmanova V et al. Increased neoplasm development due to immunosuppressive treatment with FK-506 in BALB/C mice persistently infected with the mouse herpesvirus (MHV-72). Viral Immunol 1999; 12: 237–247

110. Swann PF, Waters TR, Moulton DC et al. Role of postreplicative DNA mismatch repair in the cytotoxic action of thioguanine. Science 1996; 273: 1109–1111

111. Offman J, Opelz G, Doehler B et al. Defective DNA mismatch repair in acute myeloid leukemia/myelodysplastic syndrome after organ transplantation. Blood 2004; 104: 822–828

112. Buel JF, Gross TG, Woodle ES. Malignancy after transplantation. Transplantation 2005; 80: 5254–5264

113. Nagai M, Natsumeda Y, Konno Y et al. Selective up-regulation of type II iNOS–monophosphate dehydrogenase messenger RNA expression in human leukemias. Cancer Res 1991; 51: 3886–3890
posttransplantation Kaposi’s sarcoma. Transplantation 2004; 77:760–762

180. Euvrard S, Ulrich C, Lefrancos N. Immunosuppressants and skin cancer in transplant patients: focus on rapamycin. Dermatol Surg 2004; 30: 628–633

181. Kahan BD, Yakupoglu YK, Schoenberg L et al. Low incidence of malignancy among sirolimus/cyclosporine-treated renal transplant recipients. Transplantation 2005; 80: 749–758

182. Stallone G, Schena A, Infante B et al. Sirolimus for Kaposi’s sarcoma in renal-transplant recipients. N Engl J Med 2005; 352: 1317–1323

183. Euvrard S, Barrou B et al. Sirolimus conversion for patients with posttransplant Kaposi’s sarcoma. Am J Transplant 2006; 6: 2164–2168

184. Euvrard S, Morelon E, Rostaing L et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med 2012; 367: 329–339

185. Campbell SB, Walker R, Tai SS et al. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. Am J Transplant 2012; 12: 1146–1156

186. Kreis H, Oberbauer R, Campistol JM et al. Long-term benefits with sirolimus-based therapy after early cyclosporine withdrawal. J Am Soc Nephrol 2014; 15: 809–817

187. Alberu J, Pascoe MD, Campistol JM et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin-inhibitor-free immunotherapy: 24-month results from the CONVERT trial. Transplantation 2011; 92: 303–310

188. Ekberg H, Bernasonci C, Noldeke J et al. Cyclosporine, tacrolimus and sirolimus retain their distinct toxicity profiles despite low doses in the Symphomy study. Nephrol Dial Transplant 2010; 25: 2004–2010

189. Flechner SM, Gyida M, Cockfield S et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. Am J Transplant 2011; 11: 1633–1644

190. Budde K, Becker T, Arns W et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. Lancet 2011; 377: 837–847

191. Budde K, Lehner F, Sommerer C et al. Conversion from cyclosporine to everolimus at 4.5 months posttransplant: 3-year results from the randomized ZEUS study. Am J Transplant 2012; 12: 1528–1540

192. Budde K, Lehner F, Sommerer C et al. Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus: the randomized ZEUS study. Am J Transplant 2015; 15: 119–128

193. Yanik EL, Gustafsson SK, Kasinke B et al. Sirolimus use and cancer incidence among US kidney transplant recipients. Am J Transplant 2015; 15: 129–136

194. Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. Cancer Med 2015; 4: 1448–1459

195. Nee R, Hurst FP, Dharmidharka VR et al. Racial variation in the development of posttransplant lymphoproliferative disorders after renal transplantation. Transplantation 2011; 92: 190–195

196. Masson P, Henderson L, Chapman JR et al. Belatacept for kidney transplant recipients. Cochrane Database Syst Rev 2014; 11: 1–65

197. Vincenti F, Charpentier B, Vanrenterghem Y et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant 2010; 10: 535–546

198. Durrbach A, Pestana JM, Pearson T et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant 2010; 10: 547–557

199. Vincenti F, Larsen CP, Alberu J et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant 2012; 12: 210–217

200. Rostaing L, Vincenti F, Grinyo J et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant 2013; 13: 2875–2883

201. Vincenti F, Rostaing L, Grinyo J et al. Belatacept and long-term outcomes in kidney transplantation. N Engl J Med 2016; 374: 333–343

202. Grinyo JM, Del Carmen RM, Alberu J et al. Safety and efficacy outcomes 3 years after switching to belatacept from a calcineurin inhibitor in kidney transplant recipients: results from a phase 2 randomized trial. Am J Kidney Dis 2017; 69: 587–594

203. Penn I. The effect of immunosuppression on pre-existing cancers. Transplantation 1993; 55: 742–747

204. Kasische BL, Cangro CB, Haritharan S et al. The evaluation of renal transplantation candidates: clinical practice guidelines. Am J Transplant 2001; 1: 3–95

205. Knoll G, Cockfield S, Blydt-Hansen T et al. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. Can Med Assoc J 2005; 173: S1–S5

206. Campbell S, Filmore H, Gracey D et al. KHA-CARI guideline: recipient assessment for transplantation. Nephrology 2013; 18: 455–462

207. Batabyal P, Chapman JR, Wong G et al. Clinical practice guidelines on wait-listing for kidney transplantation: consistent and equitable? Transplantation 2012; 94: 703–713

208. Kasische BL, Vazquez MA, Harmon WE et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol 2000; 11: S1–S86

209. European best practice guidelines for renal transplantation. Section IV: long-term management of the transplant recipient. Nephrol Dial Transplant 2002; 17: 1–67

210. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9(Suppl 3): S1–S155

211. Bia M, Adey DB, Bloom RD et al. KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Kidney Dis 2010; 56: 189–218

212. Knoll GA, Blydt-Hansen TD, Campbell P et al. Canadian Society of Transplantation and Canadian Society of Nephrology commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Kidney Dis 2010; 56: 219–246

213. Baker R, Jardine A, Andrews P. Renal Association clinical practice guideline on post-operative care of the kidney transplant recipient. Nephron Clin Pract 2011; 118: c311–c347

214. Chadban SJ, Barraclough KA, Campbell SB et al. KHA-CARI guideline: KHA-CARI adaptation of the KDIGO clinical practice guideline for the care of kidney transplant recipients. Nephrology 2012; 17: 204–214

215. Acuna SA, Huang JW, Scott AL et al. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. Am J Transplant 2017; 17: 103–114
216. Schwarz A, Vatandaslar S, Merkel S et al. Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. Clin J Am Soc Nephrol 2007; 2: 750–756
217. Vajdic CM, McDonald SP, McCredie MR et al. Cancer incidence before and after kidney transplantation. JAMA 2006; 296: 2823–2831
218. Wong G, Howard K, Webster AC et al. Screening for renal cancer in recipients of kidney transplants. Nephrol Dial Transplant 2011; 26: 1729–1739
219. Wong G, Howard K, Craig JC et al. Cost-effectiveness of colorectal cancer screening in renal transplant recipients. Transplantation 2008; 85: S32–541
220. Wong G, Howard K, Webster A et al. The health and economic impact of cervical cancer screening and human papillomavirus vaccination in kidney transplant recipients. Transplantation 2009; 87: 1078–1091
221. Acuna SA, Sutradhar R, Camacho X et al. Uptake of cancer screening tests among recipients of solid organ transplantation. Am J Transplant 2017; 17: 2434–2443
222. van Leeuwen MT, Webster AC, McCredie MR et al. Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ 2010; 340: c570
223. Khokhar NZ, Altman JK, Platanias LC. Emerging roles for mammalian target of rapamycin inhibitors in the treatment of solid tumors and hematological malignancies. Curr Opin Oncol 2011; 23: 578–586
224. Baldo P, Cecco S, Giacomin E et al. mTOR pathway and mTOR inhibitors as agents for cancer therapy. Curr Cancer Drug Targets 2008; 8: 647–665
225. Cheung CY, Lam MF, Chu KH et al. Malignancies after kidney transplantation: Hong Kong renal registry. Am J Transplant 2012; 12: 3039–3046