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

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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

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risk factor, as it decreases the immunologic control of oncogenic viral infection and cancer immunosurveillance [4, 6]. Although it is accepted that the overall immunosuppressive dose is associated with the increased cancer risk following transplantation, the contributive effect of different immunosuppressive agents is not well established at this time. Currently available immunosuppressive agents influence different anticancer pathways and mammalian target of rapamycin (mTOR) inhibitors have been reported to have a decreased cancer risk compared with alternative immunosuppressive therapies. However, recent studies have not been able to demonstrate improved survival in kidney transplant recipients taking mTOR inhibitors. T cell–depleting agents are very potent immunosuppressive agents used as induction therapy and to treat acute rejection (AR) in kidney transplant recipients. While some studies have suggested an association between antibody induction and cancer after transplantation [7–11], others have failed to demonstrate this association [12–15].

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 cancer cases per 100 000 person-years [3]. The majority of the patients included in these studies were kidney transplant recipients [27]. It is important to note that this increase is not uniform for all cancer types; some cancers are not increased following kidney transplantation, e.g. breast, prostate, ovarian, cervical and brain cancers [3, 4, 20], and the incidence of breast cancer might even be reduced [3, 28]. In contrast, lymphoma, lung cancer, colon cancer, melanoma and non-melanoma skin cancer and liver cancer are increased 2- to 4-fold. In a study by Engels *et al.* [3], skin cancer was the most common malignancy in solid organ transplant recipients, with a SIR for Kaposi sarcoma and non-melanoma skin cancer of 61.46 and 13.85, respectively. In addition, the SIRs for non-Hodgkin and Hodgkin lymphoma, liver cancer, gastrointestinal cancer and melanoma were also increased [3]. In more recent reports from both the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) registry [29] and European and North American registries [23], excluding non-melanocytic skin cancers, genitourinary tract cancers are the most frequent malignancies in renal transplant recipients.

In an analysis of the Collaborative Transplant Study (CTS) database, the incidence and impact of malignant lymphoma after solid organ transplantation in 195 938 solid organ transplant recipients (145 104 cadaveric kidney transplant recipients) between 1985 and 2001 were studied [30]. Over the 10-year observation period, the risk for malignant lymphoma in renal transplant recipients was 11.8-fold higher compared with a matched non-transplanted population, and most lymphomas occurred in the first post-transplant year [30]. Recent data suggest that from 2005 to 2010, the 5-year incidence of post-transplant lymphoproliferative disease (PTLD) in adult kidney transplant recipients has remained stable [31]. There was, however, a substantial decline in PTLD rates for paediatric recipients reported in patients transplanted from 2002 to 2012 compared with those transplanted from 2000 to 2009 [31]. In all groups, PTLD risk was highest in Epstein–Barr virus (EBV)-seronegative recipients [31]. In kidney transplant recipients, there is a slight predilection for the lymphoma to occur in the transplanted kidney. In addition, central nervous system lymphomas were most common after renal transplantation in the CTS [30].

On average, the age at diagnosis of post-transplant cancer is 40 years and the time from transplantation is 3–5 years [12, 28, 32]. However, these numbers vary substantially according to the cancer subtype, with lymphoma and Kaposi sarcoma occurring early after transplantation [30, 33] and epithelial cancers later on [33, 34]. Although in other types of solid organ transplantation cancer tends to occur in the transplanted organ, in kidney transplant recipients, kidney cancers almost exclusively occur in the native kidneys [1] and there is a greater incidence of papillary type relative to the general population [35]. Acquired cystic kidney disease is common in patients with advanced renal failure and is associated with the development of kidney cancer [25, 36]. In dialysis patients, the risks for thyroid cancer, myeloma and urinary tract cancers are increased, and this is mirrored in kidney transplant recipients [25]. This parallel between dialysis patients and kidney transplant recipients does not hold true for all cancer types, as ovarian and prostate cancer were less frequent in kidney transplant recipients than in the dialysis cohorts [23].

Pathogenesis and transplant-specific risk factors

Several factors have been linked to the increased incidence of malignancies among transplant recipients [6], including age, 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 underreported 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 choriocarcinoma seems to be associated with high transmission risk and death and organs from such donors should not be accepted

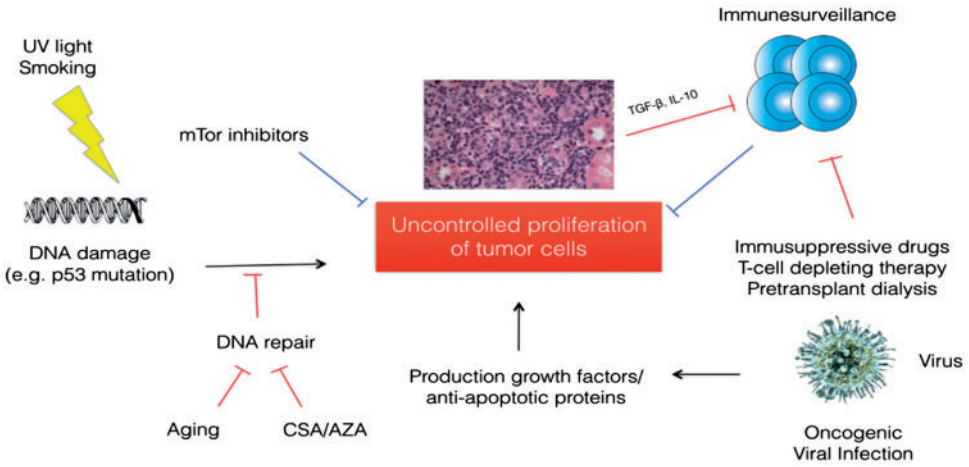

Fig. 1. Cancerogenesis following kidney transplantation (adapted from Riella [37]).

Table 1. Risk factor for post-transplant malignancies

Patient-related risk factors	Recipient age
	Previous cancer
	Sun exposure
	Viral infection
	Duration of dialysis
Transplant-related risk factors	Donor transmission
	Donor type
	Rejection
Medication-related risk factors	Net immunosuppression
	Induction therapy
	Maintenance therapy

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 $\leq$6 weeks of transplantation) was associated with a better outcome compared with late donor-transmitted cancer [51]; 5-year survival was 83% for kidney recipients with donor-transmitted cancer compared with 93% for recipients without donor-transmitted cancer ($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

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 radiofrequent 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 lymfoproliferative disorders in HSV-infected mice [104]
Azathiopurine	Inhibition of DNA and RNA synthesis through incorporation of thiopurine analogues	Intercalation at the DNA level, inhibiting repair splicing and eliciting codon misreads [105] Increased development of microsatellite DNA instability [106]
Mycophenolate mofetil	Inhibition of inosine monophosphate dehydrogenase and *de novo* purine biosynthesis	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]
mTOR inhibitors	Inhibition of mTOR pathway	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] 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]. 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 [14, 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 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 a 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 [106].

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 [14]. 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 hyperlipidemia) 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 $\leq$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]. Solid organ transplant recipients with fewer co-morbidities, assessment by a primary care provider and continuity of care by a transplant specialist at a transplant centre were associated with higher rates of becoming screen up to date in this study [221].

Table 3. Recommendations for waiting times after cancer [203–206]

Decisions regarding waiting time should be individualized and it should be expalined to all patients with a history of cancer that they are at increased risk of *de novo* malignancy post-transplantation. Recommended waiting periods before transplantation do not guarantee no recurrence of malignancy after transplantation

Absolute contraindication for transplantation
- Uncontrolled or untreated malignancies
- Multiple myeloma
- Advanced breast cancer (Stage III or IV)
- Colorectal cancer (Stage D)
- Advanced prostate cancer (Grade 4 or 5, T3c, T4, N+, M+)

No waiting time
- Superficial bladder cancer
- Non-metastatic, basal cell carcinoma
- Prostatic cancer microscopic (focal, microscopic low-grade (Gleason's grade $\leq$3), low risk) (T1a, T1c) disease
- Incidentally discovered T1 renal cell carcinoma (with no suspicious histological features)
- Monoclonal gammopathy of undetermined significance

2-year waiting time
- Invasive bladder cancer
- *In situ* breast cancer
- Localized cervical cancer
- Duke's Stage A and B1 colorectal cancer
- Hodgkin's lymphoma, non-Hodgkin's lymphoma, post-transplant lymphoproliferative disorder, leukaemia
- *In situ* melanoma
- Lung cancer
- Prostatic cancer
- Testicular cancer
- Thyroid cancer
- Wilm's tumour (a 1-year waiting period might be acceptable)

5-year waiting time
- Stage II breast cancer
- Extensive cervical cancer and non-*in situ* cancer of the uterus
- Colorectal cancer Stage C
- Melanoma
- Large or invasive or symptomatic renal cell carcinoma

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

Table 4. Recommendations for post-transplant cancer screening

Guideline	Skin cancer	Cervical cancer	Breast cancer	Colorectal cancer	Prostate cancer	Liver	Lymphoma	Others
AST kidney 2000 [208]	Self-screening Annually	Annually including PAP	Every 1–2 years	As in general population	Annually PSA and DRE	Every 6–12 months AFP and US	Clinically every 3 months in first year	Annually prostate, lung and bladder
EBPG 2002 [209]	–	Annually including PAP	Recommended	Recommended	Annually PSA and DRE	–	–	Annually prostate and kidney
KDIGO 2009 [210]	Self-screening Annually	As in general population	As in general population	As in general population	–	Annual AFP and US	–	–
NKF 2009 [211]	Annually	–	–	–	–	–	–	–
CST and CSN 2010 [212]	Self-screening Annually	Annually PAP	As in general population	As in general population	–	Annual AFP and US	–	–
RA 2011 [213]	Self-screening Annually	As in general population	As in general population	As in general population	–	–	–	–
KHA-CARI 2012 [214]	Self-screening Annually	Annually	–	–	–	–	–	–

DRE, digital rectal examination; AFP, Alpha fetoprotein; US, Ultra sound examination; PAP, PAP-mean

ceased or reduced) [222]. 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 Kiberd *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.

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