

CANCER AFTER KIDNEY TRANSPLANTATION

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*I recommend in to my son Mózes and of course my parents Erzsébet Seprényi
and Béla Borda.*

„Soli Deo Gloria”

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1. INTRADUCTION

Cancer is the second most common cause of mortality and morbidity in kidney transplant recipients after cardiovascular disease. Kidney transplant recipients have at least a twofold higher risk of developing or dying from cancer than the general population.

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, 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 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].

2. EPIDEMIOLOGY

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, 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].

3. 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].

Table 1. Risk factor for post-transplant malignancies

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

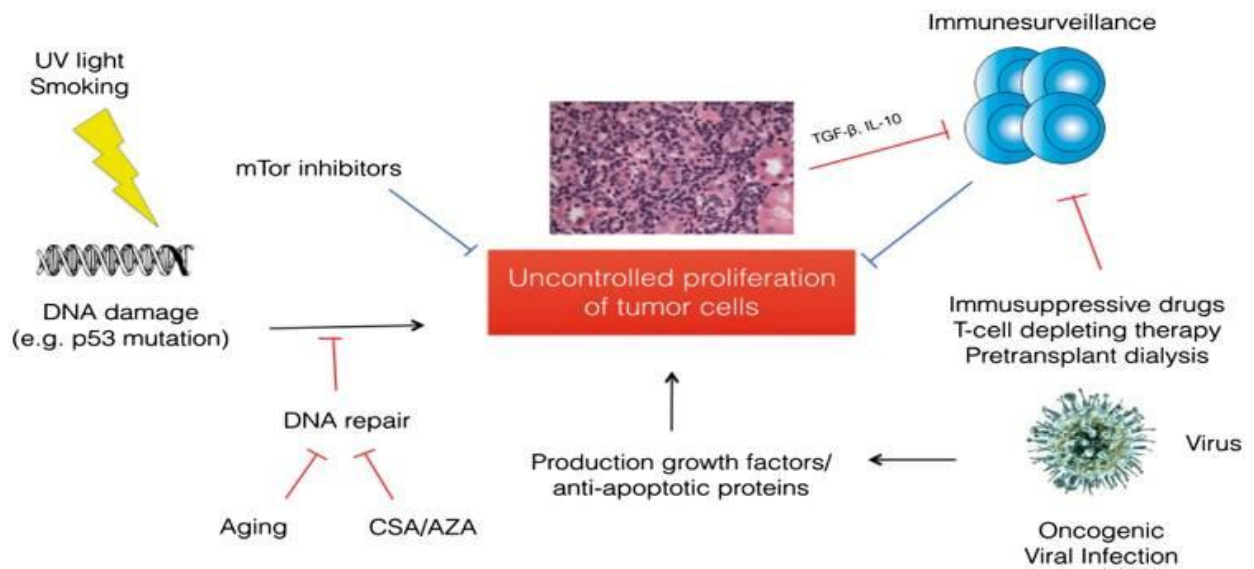


Figure 1. Cancerogenesis following kidney transplantation (adapted from Riella)

4. 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 choriocarcinoma 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].

5. DONOR AND RECIPIENT

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 PTLN [53].

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].

6. 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.

7. 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].

8. 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].

9. 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].

10. 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].

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	<ul style="list-style-type: none"> • 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]

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]

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 [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.

11. 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 anti-tumour 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].

12. 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 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].

13. TYPES OF CANACER

I. SKIN CANCER

Transplant patients are three times more likely than other people to get skin cancers after a transplant. This makes it very important for people who have had a transplant to use a strong 'sun block' cream to avoid sunburn. Exposure to the sun greatly increases the risk of developing skin cancer. In Australia, where skin cancer is particularly common, the increased risk to transplant patients rises to 40 times the average. Provided that skin cancers are diagnosed in good time, they are not usually a major problem. This type of cancer does not usually spread to other parts of the body, and can be easily removed.

There is a possibility that an anti-rejection drug called sirolimus has an additional effect against cancer, and that a switch to sirolimus should be made if someone with a transplant gets a skin cancer. Most doctors will at least reduce the doses of anti-rejection drugs overall if someone has a skin cancer.

The average duration of each dialysis period was similar, as was each period of functioning transplant. However, given the data suggesting prolonged alterations in DNA repair mechanisms associated with calcineurin inhibitors such as cyclosporin, it is likely that immunosuppression has a lasting effect on cancer development even after withdrawal. Tacrolimus-based regimens were associated with a lower incidence of NMSC in the present study compared with cyclosporin. This may be a specific effect but could also be owing to a period effect, with longer follow-up and therefore higher ascertainment of NMSC in the cyclosporin group. In the Irish national kidney transplant program, tacrolimus use in preference to cyclosporin as the initial calcineurin inhibitor in kidney transplantation began in 1996 and rose progressively to complete replacement of

cyclosporin for this purpose by 2003 onward. A very similar pattern is seen for the introduction of mycophenolate in preference to azathioprine as the initial antimetabolite in the Irish national kidney transplant program.

Some recent studies have suggested a lower risk of squamous cell carcinoma with mycophenolate-based regimens vs azathioprine in maintenance transplant immunosuppression, which may coincide with a switch to tacrolimus from cyclosporin.^{13,14} This is also substantiated by in vitro evidence suggesting an attenuation of UV radiation–induced DNA damage with a switch from azathioprine to mycophenolate in kidney transplant recipients.

II. LYMPHOMA

A small number (2-5%) of transplant patients develop a more serious cancer called lymphoma, sometimes also called ‘post transplant lymphoproliferative disease’ (PTLD). This cancer is the growth of white blood cells in the body’s immune system (mainly in the spleen and lymph nodes). Lymphoma is a very serious complication of transplantation. There are several lines of treatment, and the needs of each affected individual will need to be carefully assessed by kidney specialists and lymphoma specialists. Some lymphomas will go away if the anti-rejection drugs are stopped, there is a risk that rejection of the transplant will occur but this is not always the case. Some lymphomas will respond to drugs (chemotherapy) or X-ray treatment (radiotherapy), and anti-rejection drugs can be continued, perhaps in a reduced dosage.

III. CERVICAL AND BREAST CANCER

Women are at increased risk of cervical cancer after a transplant. Checks for cervical cancer with cervical smears should be performed at the same intervals

as suggested for the general population in women with transplants. A cervical smear is a small sample rubbed off the surface of the cervix, requiring a quick internal examination of the vagina. Older women, who are post menopausal, may not need regular cervical smears but should report any vaginal bleeding to their doctors. Cervical cancer can be detected in the very early stages by cervical smears and should be almost entirely preventable.

Breast cancer occurs at about the same rate in transplant patients as in the general population. However, because breast cancer is quite common, transplant patients should pay particular attention to their breasts, with self examination and attendance at breast screening clinics. In addition, research has shown that transplant patients commonly develop non-cancerous breast lumps, but even if these turn out to be false alarms, it is vital to get any abnormalities checked out by your doctors.

We also found that women with CKD and within the highest-income quintile were more likely to receive breast and cervical cancer screening. This is not surprising, because differences in socioeconomic status in cancer screening are well documented and may not necessarily reflect barriers, such as direct costs, but may include a lack of knowledge about the importance of early detection, cultural differences, and new immigration (20). The relatively low uptake of cervical cancer screening in the young and at-risk dialysis and transplanted population was also expected. A study in the United Kingdom reported <10% of the transplant population of women followed recommended guidelines for cervical cancer screening (21).

Cancer screening in people with chronic illness, including CKD, is complex. CKD not only increases the risk of cancer but is also a predictor of poor outcomes, driven largely by breast and urinary tract cancers (5). Despite this, literature suggests that routine screening should be avoided in patients on

dialysis and those not on the transplant donor waiting list because of reduced life expectancy and therefore, lower likelihood of screening benefit, even if cancer was diagnosed early (7,8). Routine screening in those with limited life expectancy not only has health care resource use implications but may also induce harms through subsequent diagnostic investigations, overdiagnoses, and overtreatment.

Our findings regarding the current cancer screening patterns within this large population are consistent with the recommendations by the Choosing Wisely campaign endorsed by the American Society of Nephrology and other specialty colleges worldwide (22). This initiative aims to improve patient safety and quality care and reduce wasteful resources and unnecessary tests, which may lead to more harm than benefits in patients with chronic diseases. The lower screening rates, particularly for those with comorbidities and those on dialysis, may also reflect patients' preferences for preventive medicine in the context of chronic illness (23). Apart from cancer, women with CKD have other related comorbidities with shared risk factors, including diabetes, hypertension, cardiovascular disease, and peripheral vascular disease, and over 40% of those with ESRD have more than three comorbidities (24). This is particularly relevant for older women, many of who may have underlying cognitive impairment (25,26) and may not have the ability and resources to cope with complex disease management. A previous study reported cancer prevention and screening as low priority to those on dialysis, and an over-riding attention to CKD care was observed (27).

On the contrary, younger women with kidney transplants should be encouraged to undertake routine screening and a proactive approach to preventive health care. Younger women on dialysis or who have received a kidney transplant are at increased risk of cancers. Population-based studies have reported excess risks

of cervical cancers by at least 2.5 and seven times in younger women on dialysis and with kidney transplants, respectively (28). Furthermore, the risk of breast cancer-related death in women with CKD was twofold higher than in women without CKD (5). Early detection through cancer screening may modify the longer-term cancer prognoses in women with CKD. The lower rates of screening among younger women may, therefore, represent a missed opportunity to improve patient care.

14. TREATMENT OF POST-TRANSPLANT CANCER

In general, a reduction in immunosuppression is recommended for 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 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.

15. CONCLUSION

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].

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 anticancer 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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