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"Emerging concepts in managing malignancy in kidney transplant patients"

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Introduction

Kidney transplantation remains the treatment modality of choice for many patients with end stage kidney disease (ESKD) due to the improved quality of life and increased survival patients experience. Both patient and allograft outcomes, particularly cardiovascular and infection-related mortality, have improved over the years with advancements in transplant care.[1–4] Unfortunately, despite improvements in healthcare, there has been no significant change in the overall incidence of cancer amongst kidney transplant recipients (KTRs) over the last three decades and the relative burden of cancer mortality is increasing.[5,6] Cancer remains a significant cause of morbidity and mortality in KTRs conferring more than a twofold higher risk of both cancer incidence and death in KTRs compared to the general population.[7–15] This discrepancy reflects factors unique to kidney transplantation including the use of potent immunosuppression, high prevalence of oncogenic viral infections and the increased incidence of malignancy amongst patients with kidney disease. Salient issues to consider in decreasing the burden of malignancy amongst KTRs include pre-transplant recipient evaluation, posttransplant screening and monitoring, and optimal treatment strategies for the KTR with cancer. In this review, we will address cancer incidence and outcomes, approaches to cancer screening and monitoring pre- and post-transplant, as well as treatment strategies, immunosuppressive management, and multidisciplinary approaches in the KTR with cancer.

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Epidemiology and Outcomes

The increased incidence of cancer amongst KTRs has been well described. Overall incidence in KTRs compared to age-matched and gender-matched patients in the general population has been shown to be least twofold to fourfold higher.[7–12] Observational studies from national registries have shown that the overall incidence of cancer increases in correlation with increasing time from transplant with nearly a 5% incidence of cancer in the first 5 years posttransplant to more than 25% after 20 years.[8,16] The pattern of cancer type seen in KTRs differs from that of the general population with the relative risk being highest for Kaposi sarcoma (300-fold higher), followed by non-melanomatous skin cancers (NMSC; 2-40 fold), lip cancers(>10-fold), post-transplant lymphoproliferative disease (PTLD; 4-16 fold) and anogenital cancers.[7–9] While KTRs also exhibit an increased risk of many other common forms of cancer, including lung, colorectal and kidney cancer, some endocrine associated cancers, most notably breast and prostate, have not shown to be associated with increased risk in the transplant population.[7–9] Standardized incidence ratios for common cancers posttransplant are summarized in Table 1.

Once diagnosed, KTRs with cancer suffer from worse outcomes including a higher risk of death and allograft failure.[5,11,12,15,17–19] A recent study in the Australia and New Zealand Dialysis and Transplant Registry showed >2.5-fold greater risk of cancer attributable mortality than age- and gender-matched controls which was driven predominantly by *de novo* cancers relating to immunosuppression and viral infections.[11] Cancer is the third leading cause of death in KTRs, constituting up to 56% of all deaths in patients with a functioning allograft.[17] While cancer related mortality has improved over the last several decades in the general population, this trend has not been borne out in the transplant population.[5,20] A recent study by Blosser *et. al.* demonstrated that except for an improvement in non-Hodgkin lymphoma-related mortality, there has been no significant decline in either cancer incidence or mortality over the last 30 years in the United States.[5] Additionally, studies have shown that cancer-attributable mortality increases with age and time since transplantation, suggesting that cancer deaths will represent an increasing burden as KTR survival continues to improve.[5,6,9,21,22] Reasons underlying the increase in cancer mortality remain speculative and may be related to timing of presentation, differences in tumor pathobiology and aggressiveness in the setting of immunosuppression as well as differences in therapeutic approach in patients with significant comorbidities.[18,23]

When evaluating cancer incidence and mortality amongst KTRs, it is important to consider two emerging concepts in the cancer immune cycle: immunosurveillance and immunocontainment.[24] Immunosurveillance refers to the targeting of premalignant or malignant cells by the immune system to prevent or eliminate cancer prior to observable tumor formation. Immunocontainment describes the role of immune-mediated control or suppression of malignant growth after cancer diagnosis. Defective immunosurveillance in immunosuppressed KTRs can lead to an increased incidence of cancer, particularly those associated with viral infections and high tumor mutational burden *(eg* exposure to tobacco or ultraviolet radiation, defective DNA mismatch repair, etc). Similarly, defective immunocontainment may lead to an increase in cancer relapse posttransplant as well as increased cancer aggressiveness. Understanding the relative contributions of these

mechanisms in preventing and controlling site-specific cancers may give valuable insight into approaches for both screening and management of the KTR.

Pre-transplant Evaluation

Patients with history of solid organ malignancy

Evaluating cancer risk in the potential KTR is essential to avoid cancer occurrence and subsequent premature patient mortality or loss of the organ. Despite the increased risk of cancer and cancer related deaths amongst patients with ESKD, there are currently no quality primary data to inform screening strategies in this population.[25] Therefore, current guidelines recommend transplant candidates undergo routine screenings for common cancers per the guidelines for the general population.[25,26] Candidates that are at increased risk of ESKD-related cancers such as renal cell carcinoma (eg ≥ 3 years dialysis vintage, family history of renal cancer, or acquired cystic disease or analgesic nephropathy) or bladder cancer (heavy smoking or high-dose cyclophosphamide) should undergo additional screening with ultrasound or cystoscopy, respectively.[25] Patients that pose a particular challenge in transplant evaluation are those with a history of pretransplant malignancy (PTM). While the overall rates of cancer recurrence after transplantation are low, occurring in <10% of patients with a prior history of cancer, KTRs with PTM have demonstrated worse overall survival, cancer-specific mortality and incidence of posttransplant *de novo* malignancy.[25,27–31] Clinical practice guidelines for recipient selection attempt to guide providers in balancing the benefit of equitable access to life-saving transplantation against the risk of harm due to cancer recurrence and related mortality to ensure the fair distribution of a scarce resource. These concerns have led to fixed pretransplant wait-times typically between 2-5 years based on limited quality evidence.[32] Current guidelines recently published by the Kidney Disease: Improving Global Outcomes (KDIGO) global panel in 2020 emphasize that timing of kidney transplantation after potentially curative treatment for cancer is dependent on the cancer type and stage at initial diagnosis with recommended wait times between 2-5 years based on prior data which showed a decrease in cancer recurrence with time (Table 2).[25,33] However, recent improvements in cancer treatments and prognosis have led some to re-evaluate clinical practice guidelines to better reflect recent advancements in cancer genomics and treatments. An expert consensus conference held by the American Society of Transplantation (AST) generally recommended less restriction in access than previous guidelines based on the estimation that a predicted 5-year survival of 80% is a reasonable threshold at which to offer transplantation to an individual with prior cancer.[34,35] However, these expert opinion recommendations are severely limited by a paucity of data in the transplant population and are extrapolated almost entirely based on cancer outcomes from the general population. Consequently, there is concern that these recommendations do not adequately consider the contribution of immunocontainment in apparent cancer-free survival and therefore fail to account for transplant-related abrogation of immune control over residual subclinical foci of malignancy leading to increased cancer recurrence and cancer-related mortality.[36] One novel strategy to address these concerns and better predict cancer recurrence and timing of transplant eligibility in candidates with PTM is the use of cancer genomic profiling. The rapid advancement in genome sequencing technology has led to the development of commercially available molecular assays for early

stage breast cancer to identify high- and low-risk tumors and predict risk of recurrence.[37,38] The recent MINDACT trial (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) conducted in more than 6000 women reported that patients with low genomic risk have excellent 5-year outcomes (98% and 94.7% 5-year distant metastasis-free survival in patients with low and high clinical risk, respectively).[39] Similar assays for colorectal, prostate and lung cancer are also under investigation. Given the important role in clinical decision making that genomic profiling can have in the general population, the new KDIGO guidelines have recommended the use of genomic profiling in relevant cancers to supplement prognosis estimates in candidate evaluation.[25] Application of these assays to kidney transplant candidates has the potential to identify low-risk patients eligible for immediate transplant, thereby reducing morbidity and mortality for those otherwise fated to remain on the waiting list with an inactive status.[40]

Patients with a history of plasma cell dyscrasias (monoclonal gammopathy, multiple myeloma), other hematological malignancies and hematopoietic stem cell transplant (HSCT)

More systematic, cancer- and stage-specific data is needed before personalized risk-benefit evaluations can guide high-risk listing decisions in candidates with PTM. This is particularly important for patients with hematologic malignancies, such as multiple myeloma and other plasma cell dyscrasias, as these patients are at risk for developing CKD and dialysis dependence as a result of their malignancy and represent a significant percentage of ESKD patients with PTM. Approximately 50% of patients with multiple myeloma requiring dialysis at diagnosis will have persistent CKD and up to 12% will remain dialysis dependent despite early treatment.[41] Given the high risk of recurrence and poor survival, multiple myeloma, manifesting as either cast nephropathy or monoclonal immunoglobulin deposition disease (MIDD), has often been regarded as a contraindication to kidney transplantation.[42,43] However, advancements in treatment over the last two decades have improved overall and progression-free survival, making transplantation a viable option in those who have undergone curative therapies and achieved good response depth.[44] A recent series published on a French cohort of patients with MIDD evaluated 23 patients that had undergone kidney transplantation, 14 of which had undergone treatment and achieved hematological response prior to transplantation.[45] Of those 14 patients, disease recurrence occurred in 4 patients, only one of which lost the allograft after 5 years. Another recently published descriptive systematic review identified 36 patients with either multiple myeloma (n=33) or smoldering myeloma (n=3) that underwent kidney transplantation,12 (12/33) of which experienced a relapse of multiple myeloma and 2 (2/3) of which progressed from smoldering myeloma to multiple myeloma posttransplant.[44] At the end of the follow up period, 25 (69%) were alive, of which 21 (58%) had a functioning kidney allograft. Of the 11 (31%) patients that died, only 1 death was attributed to progressive multiple myeloma and 3 due to *de novo* malignancies.[44] Another report of 4 patients with a plasma cell dyscrasia who underwent hematopoietic cell transplant followed by kidney transplant also demonstrated favorable outcomes.[46] These findings support the notion that kidney transplantation may be a viable treatment option in select patients who have achieved stable remission. The new KDIGO guidelines incorporate these observations and recommend that patients with multiple myeloma not undergo kidney transplantation unless

they have undergone potentially curative treatment and are in stable remission. A recent expert consensus conference held by the AST also delineated criteria for safe kidney transplantation in candidates with a prior history of myeloma which included stringent complete response as measured by monoclonal proteins and bone marrow plasma cells as well as the absence of a high-risk genetic profile (e.g. deletion(17p), t(4;14), or t(14;16)), good performance status, and hematologic remission >6 months.[35]

Despite being on the same disease spectrum as multiple myeloma, monoclonal gammopathy of unknown significance (MGUS) and smoldering myeloma are not considered contraindications to transplantation. These entities are pre-malignant lesions that confer a risk of malignant transformation in the general population of about 1-1.5% annually in MGUS and ~8-10% annually for the first 5 years before tapering to ~3% annually in smoldering myeloma.[25] The risk of transformation into multiple myeloma after kidney transplantation, however, is unknown and there are currently no convincing evidence that these pre-malignant lesions are at higher risk of disease progression compared to KTRs without MGUS.[47] Furthermore, there is no clear consensus on how these patients should be managed regarding definitive treatment prior to transplantation to prevent disease recurrence in the allograft or malignant transformation. As it currently stands, candidates with MGUS or smoldering myeloma are not excluded from kidney transplantation, however the risks of malignant transformation should be considered and discussed.

Hematopoietic stem cell transplantation (HSCT) is often performed as part of the curative therapeutic approach for hematologic malignancies. It is common to develop chronic kidney disease after HSCT and it could be advanced to ESKD. Several case series have reported favorable outcomes in kidney transplantation after HSCT.[46,48] A recent case series by Dominguez-Pimentel *et. al.* which included four patients who received an autologous HSCT for treatment of plasma cell dyscrasia reported stable allograft function in all recipients and no episodes of rejection.[46] Another case series and literature review of sequential allogenic HSCT and kidney transplantation also suggested an excellent graft survival (death-censored graft survival 100%) after a median 27-32 months of observational period.[48] While the number of cases was small and difficult to derive conclusions from, they also reported that the incidence of malignancy after sequential HSCT and kidney transplantation was 5% (n=1 out of 19, thyroid papillary carcinoma) in patients who received a kidney transplant from the same HSCT donor, compared to 18% (n= 2 out of 11, vaginal carcinoma and post-transplant lymphoproliferative disorder) in patients who received a kidney transplant from a different HSCT donor.[48] One interesting aspect of sequential allogeneic HSCT and kidney transplantation from the same donor is the potential for tolerance induction and avoidance of long-term immunosuppression.[49,50] A recent multicenter observational analysis comparing 22 tolerized KTRs (sequential allogeneic HSCT and kidney transplantation from the same donor) and to 20 conventional matched KTRs showed that the tolerized recipient group had stable allograft function with no incidence of graft loss and significantly lower serum creatinine levels compared to controls.[51] These excellent outcomes were partly driven by stringent HLA matching between HSCT donor and recipient, as most of tolerized cases were two-haplotype-matched transplantation. However, the superior outcome compared to the matched cohort who also had minimal HLA mismatch suggested additional immunological advantages in sequential HSCT-kidney transplant approach. Given the excellent kidney

allograft outcomes and the potential to avoid immunosuppression in recipients from the same HSCT donor, sequential allogeneic HSCT and kidney transplantation may present an attractive option in select patients, while there is currently insufficient evidence to inform whether this approach could decrease either cancer incidence or cancer-related mortality.

Post-transplant Screening and Monitoring

Despite the increased cancer incidence and mortality amongst KTRs, the value of routine cancer screening in the posttransplant population has not been adequately assessed. Given the scarcity of transplant specific evidence, most clinical practice guidelines parallel the screening recommendations for the general population in addition to regular skin examinations.[26,52] Extrapolations from the general population are unlikely to accurately reflect the cost-effectiveness of cancer screening amongst KTRs given the competing risks of death and reduced life expectancy.[52] A recent study evaluating the performance of fecal immunohistochemistry testing (FIT) for screening of colorectal cancer amongst CKD patients, including 497 KTRs, demonstrated a detection rate of 5.6% amongst KTRs with the overall test sensitivity, specificity, and positive and negative predictive values for advanced colorectal neoplasia of 0.90 (95% CI, 0.84 to 0.95), 0.83 (95% CI, 0.81 to 0.85), 0.30 (95% CI, 0.25 to 0.35), and 0.99 (95% CI, 0.98 to 1.0), respectively.[53] The sensitivity of FIT demonstrated by this study is markedly improved over that demonstrated in a previous study on 229 KTRs which showed poor sensitivity of only 0.31 with a high specificity of 0.91.[54] Another study in female transplant recipients on cyclosporin found that transplant recipients had a much higher incidence of benign breast disease on mammographic screening than the general population, suggesting that mammographic screening may lead to more harm than benefit amongst KTRs.[55] A recent systematic review of clinical practice guidelines for solid organ transplant recipients found that most guidelines did not address specific cancer screening test performance in the transplant population and merely cited screening trials conducted on the general population.[52] Only a small number of practice guidelines addressed competing causes of death and reduced life expectancy amongst transplant recipients and recommended an individualized approach to screening. Additionally, guidelines failed to include the views and preferences of important stakeholders including transplant oncologists, primary care providers, and transplant recipients.[52] Future guidelines should aim to incorporate the preferences of these stakeholders, particularly those of KTRs themselves. Despite increased contact with the healthcare system, studies have shown a decreased uptake in cancer screening amongst KTRs compared to the general population. A recent population-based study in solid organ transplant recipients in Ontario evaluating the uptake of breast, cervical, and colorectal cancer screening showed that 91.4%, 69.8%, and 77.5%, of recipients eligible for breast, cervical and colorectal screening, respectively, were not up-to-date on screening during the observation period.[56] Similarly, another Canadian cohort of patients with CKD, including 325 KTRs, showed a reduced 2-year incidence of breast cancer screening (53% in KTRs compared with 61% in the general population) as well as a reduced 3-year incidence of cervical cancer screening (60% compared with 76% in the general population).[57] Reasons for reduced uptake are likely multifactorial and may reflect limited awareness of cancer risk outside of skin cancer, prioritizing kidney health and allograft function or other immediate

health concerns above long-term cancer risk, and concern over potential harm or cost associated with screening and downstream work-up.[58–60] In addition to the conventional screening measures, circulating tumor DNA may be a potential novel tool to detect recurrent cancer more sensitively.[61,62] In non-transplant populations, circulating tumor DNA testing has been reported to predict cancer recurrence and its application in KTRs would be promising.

Treatment of post-transplant cancer

As immunosurveillance and immunocontainment are involved in the development of *de novo* and recurrent cancer, reduction of immunosuppressive agents has been a mainstay of cancer treatment in transplant recipients. Anecdotally, reduction or discontinuation of glucocorticoids or antimetabolite agents and maintenance of calcineurin inhibitors or mammalian target of rapamycin inhibitor (mTORi) is the most common approach. Azathioprine and thiazide diuretics are well described risk factors for non-melanoma skin cancers.[63–67] The large prospective observational TUMORAPA study showed that conversion from calcineurin inhibitor therapy to mTORi therapy was associated with a lower recurrence rate and longer recurrence-free survival in KTRs with a history of non-melanoma skin cancers.[68] The benefit of mTORi conversion in other solid organ transplants has also been reported.[69] However, while the benefit of risk reduction of non-melanoma skin cancer is evident, it is still unclear whether mTORi conversion is beneficial in lowering the risk of other cancers.[70–73] Also, a meta-analysis by Knoll et al. reported a 43% increased risk of death, particularly from infection and cardiovascular disease, in the patients on mTORi compared with the control group.[73] Other adverse effects of mTORi include inducing *de novo* or exacerbating pre-existing proteinuria, bone marrow suppression, hyperglycemia and post-transplant diabetes mellitus, dyslipidemia, poor wound healing, interstitial pneumonitis, and oral stomatitis.[74] A metanalysis evaluating the risk of metabolic complications on conversion of a calcineurin inhibitor-based regimen to an mTORi-based regimen in KTRs found that conversion to mTORi was associated with a non-significant trend toward increased risk of new onset diabetes after transplant (relative risk 1.32; 95% CI 0.92-1.87) and a significant increased risk of hypercholesterolemia, acute rejection, proteinuria and anemia.[75] Clinicians should be aware of the risk benefit trade-off and consider conversion to mTORi with appropriate caution.

In addition to modifying immunosuppression regimen, KTRs are eligible for most cancer-targeted therapies, including surgery, cytotoxic chemotherapy and radiation. Most KTRs have a single functioning kidney and often require a dose adjustment for cytotoxic chemotherapy. There are several cancer-directed therapies that need special consideration for kidney transplant patients and require close monitoring (see Table 3). First among these are agents known to be associated with thrombotic microangiopathy, such as gemcitabine and anti-VEGF therapies. Kidney transplant patients are often on calcineurin inhibitors and predisposed to endothelial cell injury, thus placing them at a higher risk of this complication and necessitating a higher degree of caution with use of these agents. Secondly, several commonly used immunomodulatory drugs (IMiDs) are associated with higher risk of rejection. For instance, lenalidomide, an IMiD that can directly activate T cell co-stimulation and is used for the treatment of multiple myeloma and amyloidosis,

is reported to be associated with acute rejection and is preferably avoided in transplant patients.[76–78] Similarly, IL-2 and interferon-alpha therapy are immune activating agents and known to cause acute cellular rejection and are therefore contraindicated for KTRs.[79–81] Thirdly, data on immune checkpoint inhibitor (ICI) therapy in the transplant population is now emerging. ICI therapy has revolutionized cancer management in many cancers, but the safety and efficacy concerns make its use in KTRs very challenging. The first case report by Lipson et al. suggested ipilimumab would be a safe option for transplant recipients.[82] However, accumulating data has confirmed that ICI use is associated with a very high risk of rejection (30-40%) and a high risk of allograft loss (60-80%).[83,84] Most recently, a multicenter observational study reported the safety and efficacy of the ICIs in kidney transplant patients.[85] Out of a total of 69 patients, 29 patients experienced rejection, with a median ICI initiation to rejection time of 24 days. Once rejection occurred, 65% (19) lost allograft and returned to dialysis. In biopsy-proven rejection, both acute cellular rejection and mixed cellular and antibody medicated rejection were common. Being on mTORi and 2 or 3 immunosuppressive agents were associated with lower risk of rejection.[85] Further mechanistic study of ICI-associated rejection is necessary to mitigate rejection and still achieve reasonable cancer response. Finally, chimeric antigen receptor T cell (CAR-T) therapy is a novel cellular therapy introduced for advanced lymphoma and multiple myeloma.[86–91] CAR-T cells are GMP-manufactured adoptive cells expressing an engineered chimeric T cell receptor that can bind to target cells and elicit a cytotoxic response. CAR-T therapy is known to induce cytokine release syndrome characterized by elevated inflammatory markers (CRP, ESR) and increased endothelial cell permeability.[92] This is particularly concerning for transplant recipients as the enhanced inflammatory reaction could inadvertently trigger anti-donor lymphocyte activation. Data on CAR-T use in transplant recipients is limited to only a handful of several case series reports. A case series by Krishnamoorthy *et. al.* reported poor outcomes in 3 patients with post-transplant lymphoproliferative disorder (PTLD) refractory to immunochemotherapy, all of which expired after withdrawal of care due to lack of therapeutic response to CAR-T therapy.[93] One of the patients in this series was a deceased donor kidney transplant recipient who developed sepsis and kidney failure requiring renal replacement therapy after initiation of CAR-T therapy; care was withdrawn 2 weeks after therapy due to refractory PTLD with infectious complications.[93] Another case series by Mamlouk et al. reported more positive outcomes in 3 KTRs with PTLD treated with CAR-T therapy.[94] In contrast to the prior series, immunosuppression was suspended.[94] All 3 patients survived, though 2 had disease relapse and only 1 patient experienced allograft rejection.[94] Another single center case series in 3 patients with refractory EBV-negative PTLD treated with CAR T therapy described good response to treatment, all of which survived and 2 of which achieved complete remission.[95] All 3 patients (2 KTRs, 1 liver transplant recipient) were continued on immunosuppression throughout the course of treatment and none experienced allograft dysfunction or rejection.[95] A summary of these cases is presented in Table 4.

Post-transplant Lymphoproliferative Disorder

Post-transplant lymphoproliferative disorder (PTLD) is a devastating complication post-transplantation, occurring in 1-2% of KTRs with a mortality rate of over 50%. It

encompasses a wide spectrum of clinical conditions characterized by lymphoproliferation ranging from uncomplicated mononucleosis to various forms of lymphoma.[96] It follows a biphasic pattern of distribution: the first peak occurs early within the first year of transplant and is predominantly Epstein-Barr virus (EBV) positive (>90%) and the second peak occurs later, 7-10 years after transplant, with a higher rate of EBV negative disease (~50%).[96] Early and late phase PTLD may also follow different site distributions with graft localized disease occurring early and gastrointestinal disease occurring late.[97] PTLD is most commonly of recipient origin, though graft limited disease occurring early after transplant is often donor-derived.[98] Risk factors for early PTLD include EBV-seronegativity pre-transplant and primary EBV infection, young recipient age, type of transplant (intestine>lung>heart>liver>pancreas>kidney), as well as lymphocyte depleting induction therapy; risk factors for late PTLD include duration/degree of immunosuppression, type of transplant, and older recipient age.[96,97,99,100] while controversial, many centers will use universal antiviral prophylaxis for high-risk EBV-mismatched recipients despite the lack of supporting trial evidence. Pre-emptive therapy using EBV viral load monitoring for at-risk groups is another preventive strategy as high EBV viral load often precedes clinical presentation of PTLD, allowing clinicians to intervene early with antivirals and reduction of immunosuppression. However, it should be noted there are no randomized controlled trials comparing pre-emptive strategy to placebo.[96] Once diagnosed, the treatment for PTLD is complex, though typically follows a stepwise approach starting with the reduction of immunosuppression. A single-center retrospective observational study in 67 adult solid organ transplant recipients treated with immunosuppression reduction alone as initial therapy found an overall response rate of 45% (37% complete response) and an acute rejection rate of 32%.[101] Therefore, the optimal strategy for immunosuppression reduction is unclear, though a common approach is to reduce calcineurin inhibitors by 30-50% and to stop anti-proliferative agents.[102] Escalation of management is dependent on clinical response as well as clonality, subtype and histopathologic characteristics. Most treatment strategies parallel the management of other non-Hodgkin's lymphoma, including surgical resection, radiotherapy, and anti-CD20 monoclonal antibody *(i.e.* rituximab) therapy either alone or in combination with cytotoxic chemotherapy (*e.g.* R-CHOP). A recent phase II trial investigating the efficacy of stratified consolidation therapy into rituximab or R-CHOP-21 after rituximab induction therapy found that approximately 25% of patients achieved complete response after rituximab alone and did not need chemotherapy.[102] Other treatment modalities on the horizon include adoptive immunotherapy using either donor-derived or banked third-party HLA matched allogeneic EBV-specific cytotoxic T cells (EBV-CTL).[103–105] One phase II multicenter clinical trial investigating the safety and efficacy of banked allogeneic HLA-matched EBV-CTLs in adult transplant recipients observed that EBV-CTL therapy was safe with no adverse effects and demonstrated an overall response rate (complete or partial) of 64% at 5 weeks and 52% at 6 months.[104] Another recent study in children with PTLD showed that allogeneic banked third-party EBV-CTL therapy achieved a complete response in 7 out of 11 patients and a partial response in 1 patient.[105] Given the reported high rates of PD-1 expression in infiltrating cells and PDL-L1/L2 on tumor cells in PTLD, immune checkpoint inhibitors, namely PD-(L)1 inhibitors, may present another therapeutic option for refractory PTLD, though for now should only be considered in the context of a clinical trial.[106,107]

Importance of multidisciplinary care for patients with post-transplant cancer

Transplant patients face many challenges post-transplant including pill burden, cardiovascular and infection complications, and fear of rejection. As in the non-transplant population, cancer is one of the most feared outcomes for transplant recipients. Howell et al. conducted a survey in 81 kidney transplant recipients and found that having cancer is equivalent to a few years of trade-off to graft longevity.[60] In these challenging situations of post-transplant cancer, it is extremely helpful to hold multidisciplinary conversations with the patient, primary care physician, oncologist, and transplant nephrologist, to guide patient-centered, shared decision making. Transplant oncology and transplant onconephrology are emerging subspecialty entities in post-transplant patient care. As cancer therapeutic options evolve rapidly, it would be a great benefit to have clinicians who have strong knowledge in both oncology and solid organ transplantation and accelerate multi-disciplinary discussion. Palliative care is a specialty that provides psychosocial support and helps facilitate goal-directed discussion and decision-making in the complex clinical scenario. While originally introduced and widely used in oncology field, palliative care has been shown to be effective in improving patients' quality of life and symptom burden in settings outside of oncology when introduced early in the disease management.[108,109] Post-transplant care is a highly complex and the decision-making discussions are often challenging: weighing the benefits of immunosuppression reduction or initiation of immunotherapy for cancer treatment against the risk of allograft rejection and/or failure with return to dialysis requires the input of all invested stakeholders and specialists with a high degree of coordination. In the post-transplant setting, use of an early palliative care approach is often recommended, though remains underutilized.[110,111] This likely reflects multiple contributing factors such as the intensity of care that transplant patients receive, misconception that palliative care is linked to end-of-life care, and the tendency that transplant physicians consider palliative care only after other medical treatment options are exhausted.[112] As the transplant population ages and experiences more complications, multidisciplinary approach, including collaboration with palliative care providers, should become a part of standard of care.

Concluding remarks

Cancer in kidney transplant recipients remains a huge medical and psychosocial burden in both the pre- and post-transplant setting. Despite more systematic data on diagnostics and new therapeutics, such as immune checkpoint inhibitors and CAR-T therapy, there remains an urgent unmet need to improve outcomes. A multidisciplinary approach for patients with post-transplant cancer is necessary for optimal patient-centered care and should be incorporated more into post-transplant management.

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Table 1.

Standardized incidence ratios for common cancers post kidney transplant

Region (years; number of patient)	Standardized incidence ratios (95% CI)											
	All cancers	Breast cancer	Cervical cancer	Colorectal cancer	Kidney cancer	Lip cancer	Lung cancer	Malignant melanoma	NHL	NMSC	Prostate cancer	Ref.
Canada[a] **(1981-1998; 11,391)**	2.5 (2.3-2.7)	1.3 (1.0-1.7)[b]	1.6 (0.6-3.4)	1.4 (1.0-1.8)	7.3 (5.7-9.2)	31.3 (23.5-40.8)	2.1 (1.7-2.5)	1.9 (1.2-3.0)	8.8 (7.4-10.5)	N/A	0.9 (0.6-1.3)	8
USA[c] **(NS; 113,038)**	N/A	0.95 (0.86-1.0)	1.1 (0.8-1.5)	1.2 (1.1-1.3)	6.4 (5.9-6.8)	18 (15-22)	1.6 (1.1-1.3)	2.8 (2.5-3.2)	5.9 (5.5-6.3)	N/A	0.9 (0.85-0.98)	17
USA[c] **(2007-2016; 38,130)**	1.28 (1.2-1.4)	0.62 (0.46-0.8)	N/A	0.55 (0.39-0.76)	4.94 (4.17-5.80)	N/A	0.99 (0.8-1.21)	2.43 (1.82-3.18)	3.38 (2.81-4.04)	N/A	0.68 (0.55-0.82)	5
Italy[d] **(1997-2007; 7,217)**	1.7 (1.6-1.9)[e]	0.8 (0.5-1.2)[b]	N/A	0.8 (0.5-1.2)	4.9 (3.4-6.8)	9.4 (3.1-22.0	1.1 (0.8-1.6)	1.8 (0.9-3.3)	4.5 (3.2-6.1)	N/A	1.7 (1.2-2.3)	8, Tessari 2013
Italy[f] **(1980-2011; 3,537)**	1.5 (1.3-1.8)[g]	1.2 (0.8-1.8)	8.9 (4.4-17.7)	1.2 (0.7-1.9)[h]	7.0 (5.0-9.8)	N/A	1.1 (0.1-1.7)	1.0 (0.4-3.0)	7.9 (6.0-10.5)	29.3 (26.0-33.1)	1.3 (0.8-2.1)	16
Sweden[i] **(1970-2008; 7,952)**	6.5 (6.3-6.8)	1.2 (0.9-1.8)	2.4 (1.2-4.4)	2.3 (1.8-2.9)[h]	6.2 (4.8-7.9)	46 (35-35-59)	1.7 (1.3-2.2)	2.3 (1.7-3.1)	4.8 (3.8-5.9)	121 (116-127)[j]	1.1 (0.9-1.3)	8, Krynitz 2013
UK[k] **(1980-2007; 25,104)**	2.4 (2.3-2.5)[e]	1.0 (0.8-1.2)	2.3 (1.4-3.5)	1.8 (1.6-2.1)	7.9 (6.7-9.3)	65.5 (49.9-84.6)	1.4 (1.2-1.6)	2.6 (2.0-3.3)	12.5 (11.2-13.8)	16.6 (15.9-17.3)	1.1 (0.9-1.4)	8, Collett 2010
Australia and New Zealand[l] **(1982-2003; 10,180)**	3.3 (3.1-3.5)	1.0 (0.8-1.3)	2.5 (1.3-4.3)	2.4 (1.9-2.9)[h]	5.0 (3.4-7.1)	47.1 (41.8-52.9)	2.5 (2.0-3.0)	2.5 (2.1-3.1)	9.9 (8.4-11.5)	N/A	1.0 (0.7-1.3)	7,8, Yanik 2016
Hong Kong[m] **(1972-2011; 4,674)**	2.9 (2.6-3.3)	1.7 (1.0-2.8)[b]	7.2 (3.9-13.4)	1.8 (1.2-2.5)	12.5 (8.5-18.4)	N/A	1.7 (1.2-2.4)	9.1 (2.3-36.3)	15.8 (11.9-21.0)	7.4 (4.9-11.2)	0.8 (0.4-2.0)	8, Cheung 2012
Taiwan[n] **(1997-2008; 4,716)**	3.8 (3.4-4.2)	1.1 (0.6-1.9)	0.88 (0.22-3.0)	2.0 (1.1-3.5)[i]	44.3 (36.2-54.1)	N/A	4.8 (2.7-8.5)	5.4 (0.8-38.2)	4.8 (2.6-8.9)[o]	2.3 (0.9-6.1)	1.8 (0.7-4.8)	8, Li 2012

N/A, not available; NHL, non-Hodgkin lymphoma; NMSC, non-melanoma skin cancer; NS, not-specified.

[a] Canadian Organ Replacement Registry.

[b] Female breast cancer only.

[c] US Scientific Registry of Transplant Recipients.

[d] Fifteen transplant centers in Italy.

[e] Excluding NMSC.

[f] Four transplant centers in Northern Italy

[g] Excluding skin cancers

[h] Colon cancer only.

[i] Swedish National Patient Register–Swedish Cancer Register.

[j] Squamous cell carcinoma only.

[k] UK Transplant Registry.

[l] Australia and New Zealand Dialysis and Transplant Registry.

[m] Hong Kong Renal Registry.

[n] Taiwan National Health Insurance Database.

[o] All lymphomas

Table 2.

Recommended waiting times between cancer remission and kidney transplantation

Cancer Type	Stage	Waiting Time
Breast	Early	At least 2 years
	Advanced	At least 5 years
Colorectal	Dukes A/B	At least 2 years
	Dukes C	2-5 years
	Dukes D	At least 5 years
Bladder	Invasive	At least 2 years
Kidney	Incidentaloma (<3 cm)	No waiting time
	Early	At least 2 years
	Large and invasive	At least 5 years
Uterine	Localized	At least 2 years
	Invasive	At least 5 years
Cervical	Localized	At least 2 years
	Invasive	At least 5 years
Lung	Localized	2-5 years
Testicular	Localized	At least 2 years
	Invasive	2-5 years
Melanoma	Localized	At least 5 years
	Invasive	Contraindicated
Prostate	Gleason ≤6	No waiting time
	Gleason 7	At least 2 years
	Gleason 8-10	At least 5 years
Thyroid (Papillary/Follicular/Medullary)	Stage 1	No waiting time
	Stage 2	At least 2 years
	Stage 3	At least 5 years
	Stage 4	Contraindicated
	Anaplastic	Contraindicated
Hodgkin Lymphoma	Localized	At least 2 years
	Regional	3-5 years
	Distant	At least 5 years
Non-Hodgkin Lymphoma	Localized	At least 2 years
	Regional	3-5 years
	Distant	At least 5 years
Post-transplant lymphoproliferative disease	Nodal	At least 2 years
	Extra-nodal and cerebral	At least 5 years

Adapted from the KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation.

Table 3.

Cancer-directed agents and transplant-specific concerns

Cancer-directed therapy	Complications
Gemcitabine, anti-VEGF therapy *	Thrombotic microangiopathy
IMiDs	Acute rejection
Immune checkpoint inhibitors	Acute interstitial nephritis, acute rejection and allograft loss
CAR-T therapy	Infectious complications, acute rejection

* agents known to be associated with thrombotic microangiopathy

Abbreviations: VEGF, vascular endothelial growth factor; IMiD, Immunomodulatory drugs; CAR-T, chimeric antigen receptor T cell

Table 4.

Summary of published CAR-T therapy in transplant recipients

Baseline Characteristics					Disease Characteristics at Diagnosis					Disease therapy				CAR-T adverse events and outcomes			
Series/Pt #	**Age**	**Gender**	**Organ transplanted, year**	**Posttransplant immunosuppression**	**Time from transplant (years)**	**EBV tumor Status**	**Pathology**	**Stage**	**IPI**	**1st-line therapy**	**Salvage therapy**	**Bridging Therapy**	**Immunosuppression management on CAR-T**	**CRS Grade**	**ICANS**	**Other toxicity**	**Outcome**
Krishnamoorthy et al. / Pt 1	54	M	DDKT, 1997; Pancreas, 2010	Tacrolimus, azathioprine, prednison	20	Negative	DLBCL-GCB	4	2	Rituximabalone, R-CHOP	RICE	None	Low dose tacrolimus and prednisone	1	2	AKI, acute pancreatitis, late on set FUO	Transition to hospice w/de at h at day 115 due to refractory PT LD
Krishnamoorthy et al. / Pt 2	54	F	Heart, 1992	Tacrolimus, MMF, prednisone	26	Negative	DLBCL-non GCB	4	3	R-CHOP	R-ICE	Lenalid omide	Switched from tacrolimus to sirolimus	2	3	AKI requiring RRT	Transition to hospice with de at h at day 44 due to persistent lower GI bleed from refractory PTLD
Krishnamoorthy et al. / pt 3	71	M	DDkt, 2009	Tacrolimus, azathioprine, prednisone	10	Negative	DLBCL-non GCB	4	4	R-CHOP	R-DHAX, ibrutinib	Gemcitabine and etoposide	Stopped prior	3	4	AKI requiring RRT, As pergillus Pneumonia, VRE bacteremia	Terminally extubated to comfort care, with death at day 15 from with refractory PTLD
Mamlouk et. al./ pt 1	38	M	Kidney	Tacrolimus, MMF, prednisone	10	Negative	DLBC L -GCB	4	3	R-EPOCH	R-GEM-OX	N/A	Stopped tacrolimus and MMF prior, Low dose prednisone	1	No	Allograft rejection @ week +16	CR at 1 month, sustained up to month 7
Mamlouk et. al. / Pt 2	44	M	Kidney	Sirolimus, prednisone	10	Negative	DLBCL-GCB	4	3	R-CHOP	None	N/A	Stopped prior	1	3	Pneumonia, AKI	CR at 1 month, relapsed at 34 weeks
Mamlouk et. al. / Pt 3	41	M	Kidney	Sirolimus, prednisone	7	Negative	DLBCL-GCB	4	2	R-EPOCH	R-GDP, R-ESHAP, Pola + BR	N/A	Stopped sirolimus prior, low dose prednisone	No	No	None	PR at 1 month, progressive disease at 3 month
Lutt wak et. al. / Pt 1	69	M	DD KT, 1994	Tacrolimus	25	Negative	DLBCL – GCB	4B	4	R-da EPOCH	R-GDP	Pola+BR	Stopped CNI during bridging therapy, mean tac level during	1	No	Febrile neutropenia w/bacterial infection	CR at 1 month, relapse at 3 month

Baseline Characteristics					Disease Characteristics at Diagnosis					Disease therapy				CAR-T adverse events and outcomes			
Series/Pt #	**Age**	**Gender**	**Organ transplanted, year**	**Posttransplant immunosuppression**	**Time from transplant (years)**	**EBV tumor Status**	**Pathology**	**Stage**	**IPI**	**1st-line therapy**	**Salvage therapy**	**Bridging Therapy**	**Immunosuppression management on CAR-T**	**CRS Grade**	**ICANS**	**Other toxicity**	**Outcome**
													hospitalization 4.2 ng/mL				
Lutt wak et. al. / Pt 2	50	F	DDKT, 2011	Tacrolimus	5	Negative	DLBCL – GCB	4	4	R-CHOP	R-ICE + ASCT	Gemcitabine	Stopped CNI during bridging therapy, mean tac level during hospitalization 4.1 ng/mL	2	No	Prolonged neutropenia	CR at 1 month, sustained at 3 month
Lutt wak et. al. / Pt 3	66	M	DDLT, 2011	Tacrolimus	8	Negative	DLBC L-non GCB	3	4	R-CHOP	ICE	30 Gy radiotherapy	Stopped CNI during bridging therapy, mean tac level during hospitalization 3.3 ng/mL	1	No	AKI	PR at 1 month, sustained at 3 month

Abbreviations: DDKT, deceased donor kidney transplant; MMF, mycophenolate mofetil; EBV, Epstein Barr virus; DLBCL, diffuse large B cell lymphoma; GCB, germinal center B-cell; IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone; R-ICE, Rituximab, ifosfamide, carboplatin, and etoposide; R-DHAX, Rituximab, dexamethasone, cytarabine, and oxaliplatin; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; R-GEM-Ox, rituximab, gemcitabine, oxaliplatin; GDP, gemcitabine, carboplatin and dexamethasone; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; Pola+BR, polatuzumab vedotin, bendamustine, rituximab; R-daEPOCH, rituximab, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ASCT, autologous stem cell transplantation; CNI, calcineurin inhibitor; AKI, acute kidney injury; RRT, renal replacement therapy; FUO, fever of unknown origin; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; CR, complete response; PR partial response