Immune checkpoint inhibitors in kidney transplantation

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Purpose of review
The development of immune checkpoint inhibitor (ICI) immunotherapy has revolutionized the treatment of several cancers. Malignancies are one of the leading causes of death in solid organ transplant recipients (SOTRs). Although ICI treatment may be an effective option in treating malignancies in SOTRs, concerns about triggering allograft rejection have been raised in this population. Herein, we will review currently available data regarding patients, allograft and malignancy outcomes in SOTRs who received ICI therapy.

Recent findings
Cancer incidence is three to five-fold higher among SOTRs, compared with the general population. Skin cancer is the most prevalent cancer after transplant, followed by kidney cancer, lymphoma and Kaposi sarcoma. There are no large prospective studies evaluating ICI therapy's use for treating cancers in SOTRs. However, retrospective studies have shown that ICI treatment may be associated with improved malignancy outcomes and overall survival (OS). However, the risk of allograft rejection is high (around 40%) of whom about half lose their allograft. Maintaining higher levels of immunosuppression may be associated with a lower risk of allograft rejection, but potentially worse malignancy outcomes.

Summary
Although ICI treatment may be associated with improved patient and malignancy outcomes, the risk of allograft rejection and loss are high. Prospective studies are needed to confirm the benefits of ICI therapy in SOTRs and to evaluate the optimal immunosuppression regimen modifications, if any, to improve patient, malignancy and allograft outcomes in transplant recipients.

Keywords
cancer, immune checkpoint inhibitor, immunosuppression, rejection, solid organ transplant recipients

INTRODUCTION

Suppressing the immune system is an essential strategy to prevent the rejection of solid organ transplants (SOTs). However, immunosuppression use is associated with many adverse effects in solid organ transplant recipients (SOTRs), including a higher risk of infections and malignancies. The incidence of cancer in SOTRs is three to five-fold higher than the general population [1–3], and is a leading cause of mortality in SOTRs [4,5▪]. With an increasing number of transplants performed, older age of SOTRs and improved long-term survival of SOTRs [5▪,6–8], the incidence of long-term complications of SOT, including cancer, is also increasing [9▪]. Optimizing the treatment of posttransplant malignancies to improve the outcomes of SOTRs and their allografts has become an important aspect of posttransplant care.

BACKGROUND

Treating cancers in SOTRs poses a significant dilemma as the combination of immunosuppressive regimens and chemotherapy may be associated with significant toxicity and higher risk of infections. Surgical resection alone is seldom sufficient in cancer treatment. A more recent option for the treatment of cancer is immunotherapy, particularly with immune checkpoint inhibitors (ICIs), which have been shown to be well tolerated compared with chemotherapy or radiotherapy [10▪]. However, the use of immunotherapy in SOTRs, in whom immunosuppression is the key strategy for preventing allograft rejection, is considered risky, as it could broadly unleash the immune system response,

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Curr Opin Organ Transplant 2022, 27:000–000
DOI:10.1097/MOT.0000000000001036

KEY POINTS

- Retrospective studies have shown that ICI agents are associated with durable responses in the treatment of several malignancies in kidney transplantation.
- Allograft rejection occurs in about 40% of kidney transplant recipients (KTRs) who receive ICI therapy, tends to happen within the first month after treatment in over half of cases, and is associated with allograft loss in about two thirds of those with allograft rejection.
- Prospective clinical studies are essential to determine the optimal strategy to optimize antitumor outcomes while minimizing alloimmune responses in this high-risk group.

including against the transplanted organ. Therefore, when ICI therapy was first approved by the United States Food and Drug Administration (FDA) in 2011 for anticancer therapy, SOTRs were excluded from the approval [5▪,9▪,11,12]. A closer look into the topics is presented below to better understand the dilemma and the nature of the problem.

Solid organ transplants

SOTs include kidney, pancreas, liver, heart and lung transplants. Such organs are mostly obtained from genetically nonidentical donors and the transplants are called allografts or allotransplants [13,14]. In allotransplantation, alloantigens in the transplanted tissue provoke an immune response in the recipient, which if not inhibited, could result in allograft rejection and loss. Therefore, immunosuppressive agents, including antithymocyte globulin, basiliximab, glucocorticoids, calcineurin inhibitors (CNIs), mammalian target of rapamycin (mTOR) inhibitors, antimetabolites and co-stimulation blockers, are typically used as part of a combination regimen to prevent allograft rejection. As the graft is accepted, the initial vigorous immunosuppressive therapy is gradually tapered to a less intense maintenance immunosuppressive regimen, which is continued for the rest of the patient's life [9▪,15–17].

Cancer in solid organ transplant recipients

The incidence of cancer is about three to five-fold higher in SOTRs than in the general population [1–3]. However, the higher relative incidence of different cancers is not the same. For example, skin cancer incidence has been shown to be more than 30 times higher in SOTRs compared with the general adult population. Cutaneous squamous cell carcinoma (cSCC) is by far the most common skin cancer, followed by melanoma, and Merkel cell carcinoma [18]. The reason behind the high incidence of cancer in SOTRs is multifactorial. One risk factor is the higher susceptibility to infections by carcinogenic viruses, including Epstein–Barr, human herpes viruses and hepatitis C virus, which can cause posttransplant lymphoproliferative disease, anogenital carcinoma, Kaposi sarcoma, gastric and liver cancer, respectively. Another risk factor is that immune surveillance of cancerous cells is hampered by immunosuppressive therapy, which prevents the T cells from detecting neoantigens expressed on cancer cells and eliminating them [9▪].

Immune checkpoints

James Allison in the United States and Tasuku Honjo in Japan independently discovered the immune regulatory signals that could be blocked to unleash the immune system to kill cancer cells. Allison and his group showed that antibodies that block the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) resulted in unopposed T cell activation and enhanced antitumor response [19]. This pioneering work led to the development and approval of ipilimumab, the first immunotherapeutic anticancer drug. At the same time, working independently in Japan, Tasuku Honjo discovered programmed cell death protein-1 (PD-1), another immune regulatory protein [20,21], which led to a whole new discipline of anticancer immunotherapy leading them to win the 2018 Nobel prize in Physiology and Medicine [22].

T cell activation requires multiple signals. The first signal involves the binding of the T cell receptor to antigen peptides presented on major histocompatibility complex molecules, which determines the antigen specificity of the response. In addition, a second signal is required, which involves co-stimulatory interactions between the T cell and antigen-presenting cells (APCs). These co-signalling molecules can either enhance the activation and proliferation of naive T cells or inhibit T cell activation. Several activating and inhibitory pathways have been described [23–25]. For example, the binding of CD28 on T cells to CD80/CD86 on APCs is a potent positive costimulatory signal for T cell activation. On the contrary, the binding of CTLA-4 on T cells to CD80/CD86 or the binding of PD-1 on T cells to PD-L1 on APCs are strong coinhibitory signals of T cell activation (Fig. 1).

Interaction of cancer and immune checkpoints

When anticancer immune mechanisms are active, the unique tumour antigens expressed by cancer cells are recognized and taken up by APCs, which

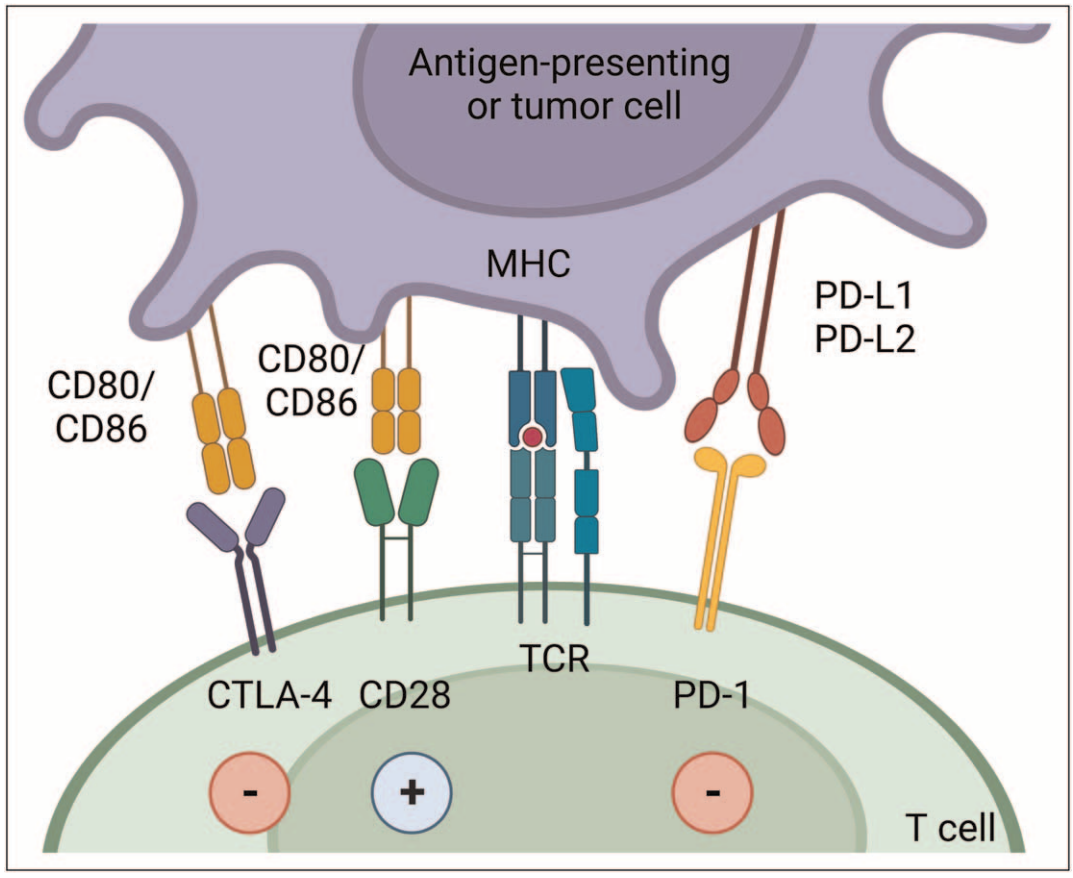

FIGURE 1. Main immune checkpoint receptors on T cells and their respective ligands. Immune checkpoints such as PD-1, CTLA-4, when bound with their respective ligands on APCs and/or tumour cells, can trigger a negative signal to T cells. CTLA-4, Cytotoxic T-Lymphocyte-Associated protein-4; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1/2, programmed cell death ligand 1/2; TCR, T-cell receptor.

then process and present peptides from the antigen to T cells to prime them. The primed T cells recognize the cancer cells by these antigens and destroy them. However, some cancers express protein ligands on their membrane surfaces, which bind to the co-inhibitory checkpoint receptors such as CTLA-4, PD-1, TIGIT, LAG-3, on the surface of the T cells and inhibit them, resulting in immune evasion [9▪,26–28]. The mechanism is illustrated on Fig. 2.

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors are antibodies designed to bind either to the checkpoint receptor on the T cell or to their ligand proteins on the surface of the cancer cells. Binding to either of them would disrupt the inhibitory signals to the T cells and unleash them [9▪,26–28] (Fig. 2).

So far, the FDA has approved eight ICIs for the treatment of a variety of cancers, summarized in Table 1 [29–35]. The cancer types that are approved for treatment with ICIs continue to increase every year, and at present, 22 types of cancer are included in the approval list [26,29,36]. The introduction of ICIs has ushered a new age in treating advanced and metastatic malignancies, as they are better tolerated and often more effective compared with chemotherapy and radiotherapy [10▪].

EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN THE TREATMENT OF CANCER IN SOLID ORGAN TRANSPLANT RECEPIENTS

In 2014, Lipson *et al.* [12] reported the treatment of two transplant recipients with ICIs leading to cancer remission, without evidence of rejection. A series of retrospective studies of treating cancers in SOTRs using ICIs followed [5▪,41–44]. These retrospective studies suggest that in SOTRs, ICI therapy stimulates the immune system sufficiently to observe significant durable clinical antitumor responses even in the setting of ongoing immunosuppression. In a study looking at the efficacy of ICI in kidney transplant recipients (KTRs), the subgroup with cSCC who received ICI therapy achieved better response

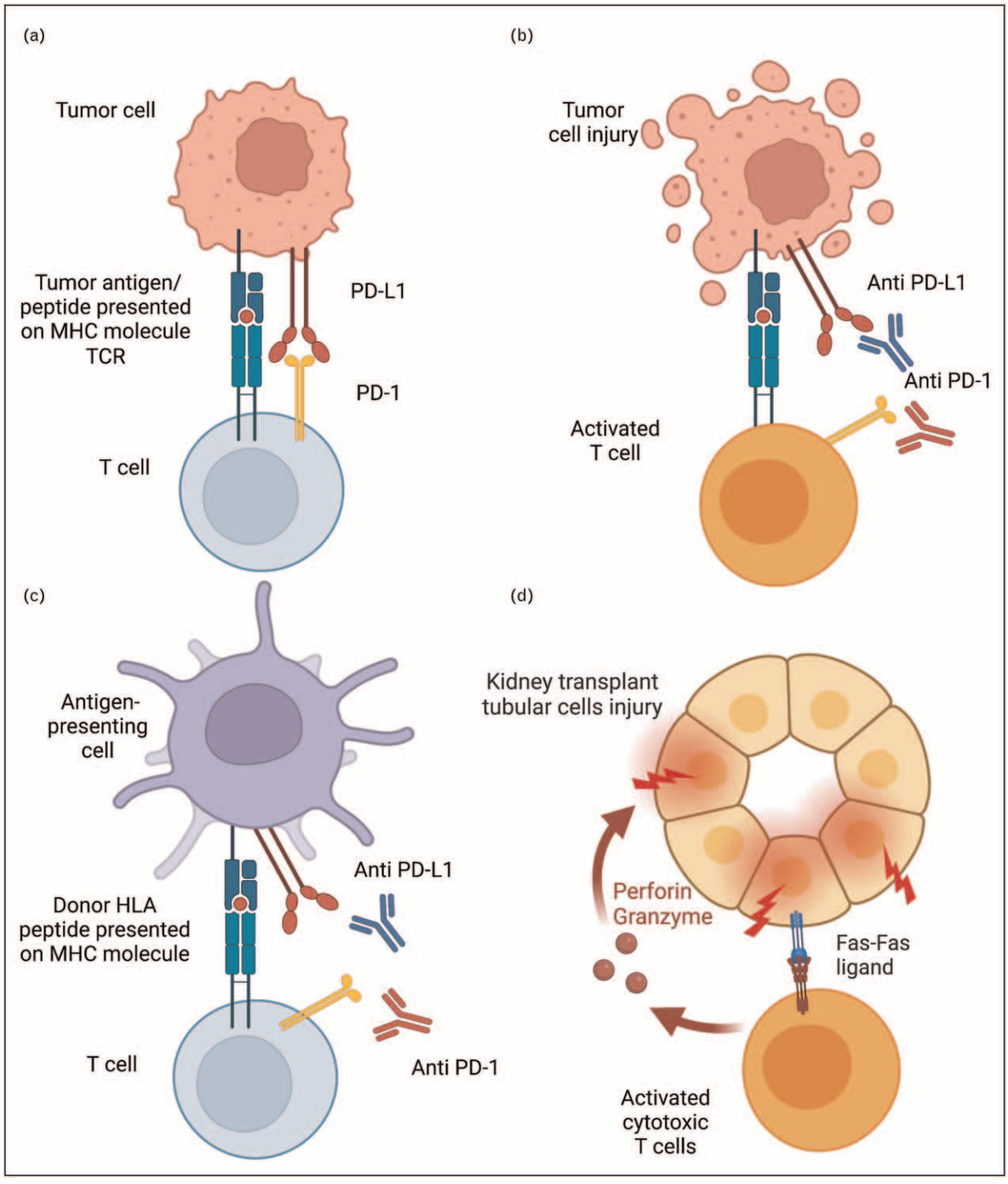

FIGURE 2. Immune evasion by tumor cells and allograft rejection. Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, keep the immune response in check. (A) The binding of PD-L1 to PD-1 provides a coinhibitory signal that prevents T cells from killing tumor cells in the body (cancer immune evasion). (B, C) Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (e.g. anti-PD-L1 or anti-PD-1) allows T cells to be activated and kill tumor cells. (D) These alloreactive T cells may recognize donor HLA peptides in transplantation and could lead to rejection. PD-1: programmed cell death protein-1; PD-L1: programmed cell death protein-Ligand 1. TCR: T cell receptor.

Table 1. Immune checkpoint inhibitors currently approved by US FDA (Please see text for citation and references)

Generic name	Target proteins	Year of FDA approval	Cancer types approved for treatment
Ipilimumab	CTLA-4	2011	Melanoma, CRC, RCC (in combination with Nivolumab), NSCLC, malignant pleural mesothelioma
Nivolumab	PD-1	2014	Melanoma, CRC, HCC, HNSCC, cHL, RCC, SCLC, NSCLC
Pembrolizumab	PD-1	2014	Cervical cancer, gastric cancer, HNSCC, CRC, HCC, HNSCC, cHL, NSCLC, MCC, DLBCL
Cemiplimab	PD-1	2018	cSCC, BCC, NSCLC
Dostarlimab	PD-1	2021	dMMR endometrial cancer, and advanced or recurrent solid tumors
Atezolizumab	PD-L1	2016	Melanoma, HCC, SCLC, NSCLC, TNBC, urothelial carcinoma
Avelumab	PD-L1	2017	MCC, RCC, urothelial carcinoma
Durvalumab	PD-L1	2017	NSCLC, urothelial carcinoma, endometrial carcinoma

Protein abbreviations: CTLA-4, cytotoxic T-Lymphocyte-Associated protein-4; PD-1, programmed cell death protein -1; PD-L1, programmed cell death protein ligand-1.
Cancer abbreviations: cHL, classic Hodgkin lymphoma; CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; DLBCL, diffuse large B-cell lymphoma; dMMR, deficient in mismatch repair; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel dell carcinoma; NSCLC, nonsmall-cell lung carcinoma; RCC, renal cell carcinoma; SCLC, nonsmall-cell lung carcinoma; TNBC, triple-negative breast cancer.

rates compared with those who those who did not receive ICI therapy (33 vs. 8.6% combined complete and partial response rate) [40▪▪]. Among potential factors associated with better response, one study found that a longer time between transplantation and ICI therapy initiation was associated with significantly higher odds of an object response rate [5▪].

Overall, the magnitude of these antitumor responses may be less compared to non-SOTRs who are not on immunosuppressive therapy, which can potentially hinder the immune-mediated antitumor effects of ICIs. For example, treatment of cutaneous melanoma using nivolumab demonstrated an objective response rate of 45% [41,42] in non-SOTRs, compared to 35.7% when the same treatment was used in SOTRs. This finding may be explained by the concept that ICI stimulation of the antitumor immune response may have been dampened by the existing immunosuppression therapy that SOTRs are on. Interestingly, this may not be the case for all tumors. For example, cSCC has the best response to ICI therapy in SOTRs at 68.2%, which is much better than the benchmark value of 34.3%-41% in non-SOTRs [5▪,38,39]. This enigmatic finding is yet to be explained and some limitations could be related to the small numbers of transplanted patients treated with ICI therapy.

Adverse events following immune checkpoint inhibitors therapy in solid organ transplant recipients

Adverse effects that are found among SOTRs that received ICI treatment can be categorized into two classes: nonimmune-related adverse events (nonirAEs) and immune-related adverse events (irAEs) [43,44]. NonirAEs include diarrhoea, fatigue, cough, nausea, skin rash, anorexia, constipation, muscle, and joint pains and infusion reactions [45]. Nonallograft-related irAEs include pneumonitis, dermatitis, colitis and hepatitis, which have been reported to occur in 37.5, 31.3, 25.0 and 12.5%, respectively [5▪]. The most feared of all complications posttransplantation is the triggering of rejection upon ICI therapy.

Allograft rejection in KTRs on immune checkpoint inhibitors

Many preclinical studies have shown a crucial role of coinhibitory signals in protecting the allograft against rejection (reviewed in [25,46]). PD-L1 expression on donor graft was essential to promote long-term graft survival [47], and blockade of PDl-PD-L1 later after transplantation could trigger rejection in tolerance models [25]. Furthermore, a preserved PD-L1 signal was also essential in fetomaternal tolerance, the most physiological scenario of tolerance in humans [48]. Although the initial report from Lipson *et al.* [12] showed that ipilimumab (anti-CLTA-4) might be a well tolerated treatment option for KTRs, nivolumab (anti PD-1) was shown to be associated with allograft rejection in 2016 [37,40▪▪]. Since then, pooled case series and meta-analyses have shown a very high rate of acute rejection of around 30–40%. Case series have shown that allograft biopsy in these patients typically shows either acute cellular rejection or mixed acute cellular and antibody-mediated rejection. More than half of allograft rejections occur within 3–4 weeks and the vast majority occur within 7 weeks of ICI initiation [5▪]. Furthermore, the risk of allograft loss in those who developed rejection is around 65%. However, there was no clear association between the development of rejection and tumour

response in one study [5▪]. Whether there is an association between rejection episodes in KTRs and overall survival (OS) is unclear.

The risk of allograft rejection and loss may differ depending on the ICI regimen used. In a multicentre study of KTRs receiving ICIs, anti-PD-L1 therapy was associated with a lower risk of rejection compared with anti-PD-1, while anti-CTLA-4 and combination ICI therapy were associated with a similar risk of rejection compared with anti-PD-1 [40▪▪]. However, in another study of SOTRs receiving ICIs, the incidences of end-stage organ failure in SOTRs who develop rejection were 50.0, 70.8 and 100.0% for anti-PD-1/PD-L1, anti-CTLA-4 and combination therapy, respectively. This may suggest that the risk of allograft loss after rejection may be higher in those who receive combination therapy. However, it is difficult to make definitive conclusions based on these studies given the small sample sizes, and prospective studies are needed.

Acute kidney injury in nontransplant patients receiving ICI therapy occurs less frequently than in KTRs, tends to happen later in the course of treatment and does not carry as grim of a kidney prognosis. Specifically, ICI-associated AKI occurs in less than 5% of nontransplant patients at a median of 14–16 weeks after therapy [23,49,50]. Low baseline estimated glomerular filtration rate, concomitant proton pump inhibitor use and combination ICI therapy have been associated with a higher risk of ICI-associated AKI [50]. Over 90% have tubulointerstitial nephritis as the dominant lesion and over 80% respond to steroid treatment [50]. The exact pathogenesis of ICI-associated AKI in native kidneys is unclear and it is believed to be an autoimmune reaction against the tubules.

The histology of biopsy of kidney transplant recipients with ICI-associated AKI has similar findings to nontransplant patients with a dominance of a mononuclear cell infiltrate involving the tubulointerstitial space [40▪▪,50]. These findings are indistinguishable from non-ICI-related acute cellular rejection or drug-associated acute interstitial nephritis, making the diagnosis and clinical management challenging. To differentiate between these three different clinical conditions at the molecular level, a gene expression analysis of the kidney biopsies was performed using NanoString, which allows the measurement of 725 immune-related gene expressions. The molecular characterization of 100 kidney biopsies revealed that the gene expression pattern of the ICI-TCMR overlaps significantly with the gene expression pattern of drug-induced or ICI-associated AIN in native kidneys compared with conventional T cell mediated rejection. Nonetheless, *FOS* and *IF127* genes were markedly elevated in ICI-TCMR compared with ICI-AIN in native kidneys [51]. Combining these two genes can possibly distinguish these two clinical conditions, and further studies may potentially help in the development of novel diagnostic and treatment strategies.

RISK FACTORS FOR ALLOGRAFT REJECTION IN SOLID ORGAN TRANSPLANT RECEPIENTS ON IMMUNE CHECKPOINT INHIBITORS

Several possible risk factors were evaluated to help risk stratify the risk of allograft rejection in SOTRs receiving ICI therapy. An interesting finding, albeit with small numbers, was related to staining for PD-L1 expression in allograft biopsies. Allograft rejection occurred more commonly in SOTRs who had expression of PD-L1 in lymphocytes within the allograft [5▪,52]. Some studies found a higher risk of allograft rejection when ICIs are given earlier after transplant [52], but other studies did not find similar association between the two [5▪,40▪▪]. Furthermore, combinations of multiple checkpoint inhibitors are likely associated with higher rejection rates. Lastly, one study showed a nonsignificant trend toward a higher risk of allograft rejection after ICI treatment in SOTRs with a prior history of rejection, but this did not reach statistical significance [5▪].

Cause of death in solid organ transplant recipients on immune checkpoint inhibitor therapy

One study evaluated causes of death among SOTRs who were treated with ICIs and found that overall progressive cancer was the most common cause of death (64%) followed by graft failure (24%). Organ-specific differences were observed in the study wherein progressive disease was the most common cause of death in KTRs (55.6%), while allograft failure was the most common cause of death in liver transplant recipients (72.7%) [5▪]. This is likely driven by the fact that KTRs with allograft failure can return to maintenance dialysis for renal replacement therapy, while liver allograft failure does not have alternative 'liver replacement' therapy. Nonetheless, patients returning to dialysis also carry a significant high mortality that surpasses many cancers. Therefore, finding the best risk/benefit ratio in treating cancer with ICI remains to be determined.

Do immunosuppressive regimens affect the outcomes of immune checkpoint inhibitor treatment?

As the efficacy of ICIs depends on the activation of the immune system, there are concerns about

whether continued or augmented immunosuppression may reduce their antitumor effects. One study found that reduction in immunosuppression was associated with over fourfold higher odds of developing an ORR compared with those who did not have their immunosuppression reduced. However, there were no specific agents or number of agents that were associated with higher odds of an ORR [5▪] and difference across various cancers likely exist.

With regards to rejection outcomes, the use of higher-dose glucocorticoids may be associated with a lower risk of allograft rejection in SOTRs on ICIs. In a small case series of KTRs, fewer rejection events occurred in those who received prednisolone in mini-pulses (20–40 mg per day) starting a day before ICI infusion and continued over 1–2 weeks), followed by a maintenance dose of 10 mg daily [53]. However, the benefit was not found in a subsequent study [40▪▪]. Portuguese *et al.* [5▪] looked at all SOTRs and found that tacrolimus use was associated with lower odds of allograft rejection after ICI therapy in the entire cohort in multivariable analysis. However, subgroup analysis showed that liver transplant recipients, but not KTRs, were less likely to develop rejection if they were on tacrolimus. In KTRs, they found that everolimus, but not sirolimus, use in KTRs receiving ICI therapy was associated with lower odds of developing allograft rejection [5▪]. These findings suggest that tacrolimus use in liver transplant recipients and everolimus use in KTRs may be a potential strategy to prevent allograft rejection, and that the effect may be specific to this medication and not necessarily be a class effect. Although any conclusion is probably confounded by differences in immunosuppression management between different SOTs. Although most centres would typically reduce maintenance immunosuppression in KTRs who develop cancer, whether this strategy is the optimal strategy in KTRs with cancer treated with ICI therapy is being evaluated prospectively. In a small prospective phase I study of maintaining KTRs on their baseline immunosuppression regimen when receiving ICI therapy, the risk of rejection was only 12%, which is significantly lower than prior estimates [54]. However, it was an uncontrolled single-arm study with only 17 KTRs, and therefore, conclusions about the effect of maintaining immunosuppression on cancer outcomes cannot be definitive.

These findings combined raise several questions that will need to be evaluated prospectively:

(1) What is the optimal immunosuppressive regimen to not interfere with ICI therapy efficacy across different cancers?
(2) What is the optimal immunosuppressive regimen to prevent allograft rejection in SOTRs? Will this regimen differ depending on the type of organ transplanted?
(3) Is there an immunosuppressive regimen that can maximize the antitumour effects of ICI therapy but minimize alloimmune responses? Or will it always have to be a tradeoff between the two?

Monitoring of KTRs on immune checkpoint inhibitor therapy

As KTRs who develop cancer frequently have their immunosuppression regimen reduced and as checkpoint inhibitor use presents an additional risk factor for rejection, KTRs on ICI therapy should have close monitoring for rejection after treatment initiation. Monitoring of routine laboratories such as serum creatinine and proteinuria should be done frequently (e.g. weekly), as the risk of rejection seems to be highest in the first few weeks after therapy. Additional monitoring with donor-specific antibodies or donor-derived cell-free DNA can be also considered for noninvasive monitoring of rejection and their potential benefits should be studied under research protocols.

CONCLUSION

Although retrospective data show that ICI immunotherapy may be associated with durable antitumour effects, the outcomes of allograft rejection, allograft loss, morbidity and mortality remain far from satisfactory. Furthermore, even if antitumour effects can be further optimized, the high risk of allograft rejection and allograft loss in SOTRs on ICI therapy remains a significant clinical dilemma. Kidney transplant recipients are, in particular, worried about the prospect of going back on dialysis after ICI therapy, as it is frequently viewed as a death sentence for many patients. Prospective clinical studies are essential to determine the optimal strategy to optimize both antitumour outcomes while minimizing alloimmune responses in this high-risk group.

Acknowledgements

None.

Financial support and sponsorship

This work was in part supported by the following research grants: National Institute of Health (NIH) Grant R01 AI143887 (to L.V.R.), the Assistant Secretary of Defense and Health Affairs, through the Reconstructive Transplant Research (RTR), under Award No. W81XWH2010758 and W81XWH2110904 (to L.V.R.).

Conflicts of interest

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense. L.V. Riella reports receiving research funding from Bristol-Meyers Squibb, Caredx, Natera and Visterra; reports serving as a scientific advisor of Veloxis; and is in part supported by the Harold and Ellen Danser Endowed/Distinguished Chair in Transplantation at Massachusetts General Hospital (Boston, MA, USA). All remaining authors have nothing to disclose.

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