

Immune checkpoint inhibitors for solid organ transplant recipients: clinical updates

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Transplant care continues to advance with increasing clinical experience and improvements in immunosuppressive therapy. As the population ages and long-term survival improves, transplant patient care has become more complex due to comorbidities, frailty, and the increased prevalence of cancer posttransplantation. Immune checkpoint inhibitors (ICIs) have become a standard treatment option for many cancers in non-transplant patients, but the use of ICIs in transplant patients is challenging due to the possibility of disrupting immune tolerance. However, over the past few years, ICIs have gradually started to be used in transplant patients as well. In this study, we review the current use of ICIs after all solid organ transplantation procedures (kidney, liver, heart, and lung). Increasing data suggest that the type and number of immunosuppressants may affect the risk of rejection after immunotherapy. Immunotherapy for cancer in transplant patients may be a feasible option for selected patients; however, prospective trials in specific organ transplant recipients are needed.

Keywords: Immune checkpoint inhibitor; Transplantation; Graft rejection; Programmed cell death protein 1; Cytotoxic T-lymphocyte-associated protein 4

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy and increasingly become a standard of care for many cancer types. The binding of ICIs to either immune checkpoint molecules or their ligands inhibits the transmission of co-inhibitory signals, enabling T cell activation against cancer cells. Since the first Food and Drug Administration (FDA) approval in 2011, eight ICIs have

been approved in the United States (US), and this number continues to grow [1]. It is currently estimated that 44% of newly diagnosed cancer patients are eligible for ICIs [2]. Solid-organ transplant (SOT) recipients were initially excluded from clinical trials of ICIs due to concerns for their safety, yielding little initial data for this patient population. The demonstrated efficacy of ICIs in non-transplant patients with cancer has motivated a gradual assessment of the efficacy and safety of ICI therapies in patients

HIGHLIGHTS

- Immunotherapy for cancer in transplant patients is becoming more common, as immunotherapy has received Food and Drug Administration approval for more cancers.
- Immunotherapy for solid organ transplant recipients is challenging due to a higher risk of rejection.
- Prospective clinical studies investigating the optimal adjustment of immunosuppressants are awaited.

with SOT. Herein, we review the potential mechanisms of ICI-associated rejection of transplanted organs and the literature on reported cases where ICIs were used in transplant recipients, and we discuss the outcomes.

MECHANISMS OF ACTION OF IMMUNE CHECKPOINT INHIBITORS TOWARD TUMOR CELLS

Tumor immunity is elicited through the cancer immunity cycle. First, when cancer cells release tumor-associated neoantigens, antigen-presenting cells (APCs) recognize and uptake the antigens. APCs then present the captured antigens on major histocompatibility complex (MHC) class I and MHC class II to T cells, resulting in their activation. Activated T cells can kill cancer cells by specifically recognizing and infiltrating the tumor microenvironment through interactions with T cell receptors and MHC I-bound cognate antigens. Repetition of this cycle occurs through the release of additional tumor-associated neoantigens upon T cell-induced cancer cell death, resulting in an increased response amplitude.

Co-inhibitory molecules, such as programmed cell death protein 1 (PD-1), programmed cell death ligand 1/2 (PD-L1/2) and lymphocyte activation gene 3 (LAG-3), play critical roles in modulating the cancer immunity cycle (Fig. 1A). When PD-1 on T cells binds to PD-L1 or PD-L2 on cancer cells or APCs, T cell activation is suppressed, causing immune escape of cancer cells. Anti-PD-1 antibodies bind to PD-1 on T cells and inhibit the binding of PD-1 to PD-L1/2, thereby blocking the transmission of inhibitory signals and restoring the anti-tumor effect. Anti-PD-L1 antibodies inhibit PD-1 interactions with T cells by binding to PD-L1 expressed on cancer and APCs.

As a result, inhibitory signaling to T cells is blocked, and T cell activation is maintained. Another ICI target includes cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which is expressed on activated T cells and regulatory T cells (Tregs). CTLA-4 inhibits T cell activation by binding to B7 (CD80/CD86) on APCs. By inhibiting the binding of CTLA-4 to B7, the anti-CTLA-4 antibody enables the binding of CD28 (a co-stimulatory molecule on T cells) to B7, thereby reactivating T cells. Additionally, LAG-3 is a cell surface molecule expressed on effector T cells and Tregs. Inhibition of LAG-3 may restore the effector function of exhausted T cells and promote anti-tumor responses. In particular, it started to be clinically used in combination with anti-PD-1 antibodies (Fig. 1A) [3,4].

CURRENT INDICATIONS OF IMMUNE CHECKPOINT INHIBITORS AND RESPONSE RATE

The FDA approval of ipilimumab (2011), an anti-CTLA-4 antibody was followed by the emergence of anti-PD-1 antibodies, which include pembrolizumab (2014), nivolumab (2014), durvalumab (2017), avelumab (2017), cemiplimab (2018), and dostarlimab (2021). With the inclusion of atezolizumab, an anti-PD-L1 antibody, eight ICI therapies have been approved for use in the US. The number of cancer types that received FDA approval for ICIs continues to increase every year, from advanced melanoma in 2011 to 22 types of cancer at present [1,5].

In 2011, only 1.5% of cancer patients were eligible for ICIs in the US. However, ICIs are now indicated in more than 40% of cancer patients as of 2022. The percentage of patients estimated to respond to ICIs was 0.14% in 2011 and increased to 12.5% in 2018 [2]. According to global statistics from 2020, there were 19.3 million new cancer cases worldwide. Adapting this percentage, roughly 7.72 million people are eligible for ICIs each year, and 2.4 million people have the potential to benefit from ICIs [6].

POSTTRANSPLANT CANCER AND IMMUNE CHECKPOINT INHIBITORS: A LITERATURE REVIEW

Kidney, liver, heart, and lung transplants are the most commonly performed SOTs. Progress in surgical techniques and advances in immunosuppressants have

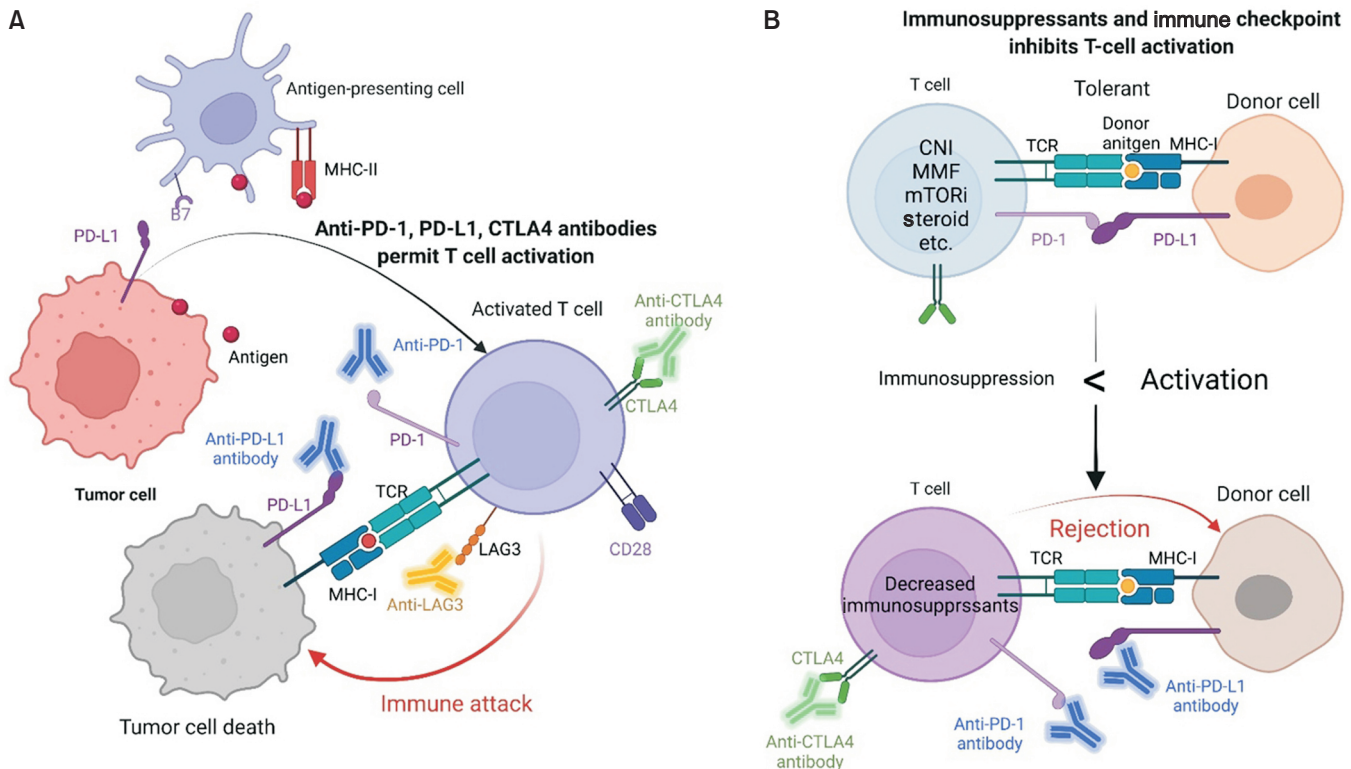


Fig. 1. (A) Mechanism of action of immune checkpoint inhibitors (ICIs). When programmed cell death protein 1 (PD-1) on T cells binds to programmed cell death ligand 1 (PD-L1) or 2 on cancer cells or antigen-presenting cells, T cell activation is suppressed, causing immune escape of cancer cells. Anti-PD-1 antibodies bind to PD-1 on T cells and inhibit the binding of PD-1 to PD-L1/PD-L2, thereby blocking the transmission of inhibitory signals, maintaining T cell activation and restoring the anti-tumor effect. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is expressed on activated T cells and Treg cells, and inhibits T cell activation by binding to B7 on antigen-presenting cells. By inhibiting the binding of CTLA-4 to B7, the anti-CTLA-4 antibody enables the binding of CD28 to B7, thereby reactivating T cells. (B) Mechanism of rejection caused by ICIs. In posttransplant patients, donor cells produce donor antigens, and immunosuppressants are used to suppress T cell activation and regulate immunological tolerance. In patients with cancer after organ transplant, a reduction in the dose of immunosuppressants is often considered to avoid overimmunosuppression and to recover adequate tumor immunity. In addition, ICIs have the potential to disrupt the equilibrium of immunological tolerance and lead to acute rejection. MHC, major histocompatibility complex; TCR, T-cell receptor; LAG3, lymphocyte activation gene 3; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor.

improved the survival of transplant recipients. As a result, the number of patients who develop cancer post-transplant is increasing over time. Importantly, the risk of cancer is much higher in transplant patients than in non-transplant patients due to their long-standing immunosuppressed state [7]. Suppression of the immune system against carcinogenic viruses and the inhibition of cancer immune surveillance can lead to the development of a variety of cancers. While most cancers posttransplant occur *de novo* after transplantation, rare causes of posttransplant cancer include the recurrence of (microscopic) cancer that was present in patients prior to transplantation or donor-derived cancer transmission [8-10].

Additionally, virus-associated cancers, most commonly caused by the Epstein-Barr virus and human herpes virus, frequently arise from the immunological suppression of many patients on allograft rejection prevention therapies. Vajdic et al. [11] reported that the standardized incidence ratio of cancer was 3.27 in post-kidney transplant patients compared to non-transplant patients. ICI use in transplant patients was first reported by Lipson et al. [12] in 2014. Since then, the number of case reports of ICI therapies in kidney and liver transplant recipients has gradually increased, and there are scattered case reports of ICI use in patients after heart and lung transplantation.

Mechanisms of ICI-Induced Rejection of Transplanted Organs

In transplant recipients, the donor cells release donor antigens and provoke an alloantigen-directed immune response. Immunosuppressants such as calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), mammalian target of rapamycin (mTOR) inhibitors, and steroids are the mainstay for suppressing T cell activation and regulating immunological tolerance. In patients with cancer after organ transplantation, the dose of immunosuppressants is often reduced to avoid over-immunosuppression and to recover adequate tumor immunity, based on their cancer type and severity. ICIs have the potential to disrupt the equilibrium of immunological tolerance and lead to acute rejection, with the frequency depending on the transplant organ type (Fig. 1B) [13].

Kidney Transplantation

Kidney transplant recipients survive for more than 15 years on average [14], and cancers associated with long-term immunosuppression are common. Although ICI use is undoubtedly challenging because of the increased risk of rejection, the largest number of ICI-treated cases was reported in kidney transplant recipients among all SOT recipients, because hemodialysis is available as a backup therapy even if rejection occurs. The most commonly reported types of cancer are cutaneous squamous cell carcinoma (cSCC) and melanoma, and there are also reports of non-small cell lung cancer (NSCLC) and renal cell carcinoma (Table 1). Our group recently conducted the largest multi-center retrospective study to understand the safety and efficacy of ICIs in kidney transplant recipients. Out of 69 patients, 29 patients (42%) experienced rejection, of whom 19 patients (66%) developed allograft failure and needed dialysis. The use of an mTOR inhibitor, a three-immunosuppressant regimen, and deceased-donor kidney transplant status were associated with a lower risk of rejection [15]. Among a subgroup analysis of a cSCC cohort (n=47), both overall survival (OS) and disease-specific survival were slightly longer in patients receiving ICI therapies than in their non-ICI recipient counterparts. In an updated literature review, 96 cases with patient-level granular data were available, of whom 46 (48%) had acute allograft rejection and 33 (72%) needed dialysis. Thirty-two patients (34%) had tumor response to treatment (partial response [PR] or complete response [CR]) (Table 1). Interestingly, Lipson et al. [16,17] reported a successful kidney retransplantation for a patient who had lost an

allograft after pembrolizumab therapy. The patient experienced severe allograft rejection 2 months after pembrolizumab therapy for cSCC. Nine months after the initiation of pembrolizumab, the patient achieved CR and pembrolizumab was discontinued. The patient maintained CR for 4.5 years and underwent a kidney retransplantation from an unrelated living donor, with one DR human leukocyte antigen mismatch. The patient received reduced thymoglobulin induction (3.0 mg/kg) and was maintained with CNI, MMF, and prednisone. The patient did not experience a rejection episode for more than 10 months post-retransplant at the time of the publication [16,17]. Pharmacovigilance studies have also reported a higher risk of allograft rejection based on Vigibase, the World Health Organization's global database of reported potential side effects of medical products. Sixty-five cases of acute allograft rejection were associated with nivolumab (the information component 025; the lower limit of a 95% credibility interval for the information component ($IC_{0.25}=1.32$), pembrolizumab ($IC_{0.25}=1.17$) and ipilimumab ($IC_{0.25}=0.33$). According to these reports, biopsy-proven rejections were mostly T-cell-mediated, whereas antibody-mediated rejection was less common [18,19]. This pharmacovigilance study approach is useful for accumulating a larger number of cases, but we should be aware of an inherent reporting bias and a high level of missing data. Therefore, prospective studies with granular patient-level data will be key to understanding the precise risk factors and immune modulation strategy.

Donor-derived cell-free DNA (dd-cfDNA) has been established as a non-invasive biomarker to assess acute rejection after a kidney transplant. dd-cfDNA has also previously been reported to have the potential for utilization in the assessment of acute rejection in patients receiving ICI therapies posttransplant [20]. Hurkmans et al. [21] reported that after initiation of nivolumab treatment for cSCC after kidney transplant, dd-cfDNA increased to 23%, which coincided with renal function deterioration and biopsy-proven acute rejection of the allograft. In contrast, Lakhani et al. [22] reported that after 10 months of treatment with pembrolizumab for melanoma, dd-cfDNA increased slightly (<0.7%) from below the detection limit (<0.19%), but did not exceed the 1% threshold suggestive of acute rejection. These findings suggest that the treatment of melanoma with pembrolizumab can be successful without evidence of allograft dysfunction or rejection. While these findings are promising, further cases are expected to be accumulated to elucidate the utility and

Table 1. Kidney transplantation cases

Study	Type of cancer	Allograft outcome	Checkpoint inhibitor	Year from tx to ICI	IS regimen	Cancer response	Interval between IS reduction and ICI initiation	ICI to rejection time
Murakami et al. (2021) [15]	cSCC 24, Melanoma 22, NSCLC 8, MCC 4, RCC 3, Bladder Ca.2, Others 6	Rejection in 29/69 (19HD)	Pembrolizumab 29, Nivolumab 11, Cemiplimab 10, Atezolizumab 3, Avelumab 3, Ipilimumab 2, Combination 11	9.33 (4.1–15.6)	Steroid, antimetabolite, mTORi, CNI, dynamic steroid+mTORi, etc.	CR 5, PR 15, SD 13, PD 34, NA 4	NA	
Lakhani et al. (2021) [22]	cSCC	No rejection	Pembrolizumab	7	Tac 8 mg+MMF 1,000 mg+Pred 5 mg → everolimus+MMF 500 mg	SD	5 mo	
Tan et al. (2021) [23]	Melanoma	Rejected, HD	Nivolumab	14	Tac+MMF+Pred → Tac+Pred	CR	10 mo	15 day
Tsung et al. (2021) [24]	cSCC	No rejection	Cemiplimabx13	NA	Everolimus+Pred	PR	NA	
	cSCC	No rejection	Pembrolizumabx2	NA	Everolimus+Pred	PD	NA	
	cSCC	Rejected, no HD	Cemiplimabx7	14.3	Tac+Pred	SD	NA	2 mo
	cSCC	No rejection	Cemiplimabx5	NA	Everolimus+Pred	PR	NA	
Kumar et al. (2020) [25]	facial SCC	Rejected, reacted pulse	Pembrolizumab	15	Tac+MMF+Pred → sirolimus+MMF+Pred	CR	NA	8 mo
	Melanoma	Rejected, reacted pulse	Pembrolizumab	11	Tac+MMF+Pred → sirolimus+MMF	SD	NA	1 mo
Trager et al. (2020) [26]	Melanoma	No rejection	Ipilimumab and nivolumab then nivolumab	3	Tac+sirolimus → sirolimus → off	PR	1 mo	
	Melanoma	Rejected, HD	Pembrolizumab then ipilimumab+nivolumab	2	Tac+MMF+Pred → Pred	PD	1 mo	1 mo
	cSCC	No rejection	Cemiplimab then ipilimumab and nivolumab	13	Tac+sirolimus+MMF → sirolimus	PR	2 mo	
	Melanoma	Rejected, reacted pulse	Nivolumab and ipilimumab	4	Sirolimus+MMF+Pred → sirolimus+Pred	SD	1 mo	
Venkatachalam et al. (2020) [27]	cSCC	Rejected, HD	Pembrolizumab	3	Tac+Pred → everolimus+Pred	PD	Concurrent	8 wk
	cSCC	No rejection	Pembrolizumab	22	CYA+MMF+Pred → CYA ↓ +Pred	PD	6 wk	NA
	RCC	AKI, no HD	Nivolumab	2	Tac+MMF+Pred → Tac ↓ +Pred → everolimus+Pred	PD	NA	6 wk
	Melanoma	No rejection	Pembrolizumab, then ipilimumab, then nivolumab	19	CYA+azathioprine+Pred → sirolimus+Pred	PD	3 mo	NA
	Melanoma	Rejected, HD	Ipilimumab, then pembrolizumab	15	CYA+azathioprine+Pred → Pred	PR	NA	3 wk
	LUAD	No rejection	Pembrolizumab	10	Tac+Pred → Pred	PD	Concurrent	NA
Hurkmans et al. (2019) [21]	Melanoma	Rejected, HD	Nivolumabx5	5	Tac+MMF → Pred 20 mg	PD	1 wk	12 day

Table 1. Continued

Study	Type of cancer	Allograft outcome	Checkpoint inhibitor	Year from tx to ICI	IS regimen	Cancer response	Interval between IS reduction and ICI initiation	ICI to rejection time
Zehou et al. (2018) [28]	Melanoma	No rejection	Ipilimumab×4	2	Tac+MMF+Pred → everolimus+MMF+Pred	PD	Just before	
	Melanoma	No rejection	Ipilimumab×4	7	Tac+MMF+Pred → sirolimus+Pred	PD	8 mo	
	Melanoma	No rejection	Ipilimumab×3 then nivolumab	6	Everolimus+azathioprine+Pred	PD	NA	
	Melanoma	No rejection	Ipilimumab×4	1	Tac+everolimus+Pred → MMF+everolimus ↑+Pred ↑	PD	1 mo	
	Melanoma	Rejected, HD	Ipilimumab×1	26	Everolimus+Pred → Pred	SD	1 mo	27 day
	Melanoma	No rejection	Ipilimumab×4	23	CYA+Pred → everolimus	PR	8 mo	
Barnett et al. (2017) [29]	Duodenum adenocarcinoma	No rejection	Nivolumab	6	Tac+MMF+Pred → sirolimus+Pred	SD	1 wk	
Kitai et al. (2017) [30]	cSCC	No rejection	Nivolumab	14	Tac+MMF → sirolimus	SD	NA	
Kwatra et al. (2017) [31]	Melanoma	Rejected, BSC	Pembrolizumab×2	13	Tac+MMF → azathioprine 100 mg daily and everolimus 0.5 mg twice	PD	1.5 mo	
Alhamad et al. (2016) [32]	Melanoma	Rejected, HD	Ipilimumab×4 then pembrolizumab	15	CYA+Pred → Pred	PD	NA	3 Weeks after pembrolizumab initiation
Boils et al. (2016) [33]	NSCLC	Rejected, HD	Nivolumab×3	5	CYA+Pred → CYA (decreased)+Pred	NA	2 yr	NA
Herz et al. (2016) [34]	Melanoma	No rejection	Ipilimumab then nivolumab	8	Tac+Pred	PD	NA	
Jose et al. (2016) [35]	Melanoma	Rejected, HD	Ipilimumab×2	16	Tac → Pred	NA	NA	1 mo
Lipson et al. (2016) [16,17]	cSCC	Rejected, HD	Pembrolizumab	25	Pred 5 mg	CR	NA	2 mo
Ong et al. (2016) [36]	Melanoma	Rejected, HD	Nivolumab	12	Tac+MMF+Pred → Pred 10 mg	PR	2 mo	8 day
Spain et al. (2016) [37]	Melanoma	Rejected, HD	Ipilimumab×4 then nivolumab	15	Tac+Pred → Pred 5 mg	PR	NA	8 Days after nivolumab initiation
Lipson et al. (2014) [12]	Melanoma	No rejection	Ipilimumab	11	Tac+Pred → Pred 5 mg	PR	6 wk	
	Melanoma	No rejection	Ipilimumab×4	8	Tac+MMF+Pred → Pred 5 mg	PD	1 yr	

tx, transplantation; ICI, immune checkpoint inhibitor; IS, immunosuppressant; cSCC, cutaneous squamous cell carcinoma; NSCLC, non-small cell lung cancer; MCC, Merkel cell carcinoma; RCC, renal cell carcinoma; HD, hemodialysis; mTORi, mammalian target of rapamycin inhibitor; CNI, calcineurin inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not applicable; Tac, tacrolimus; MMF, mycophenolate mofetil; Pred, prednisone; CYA, cyclosporin A; AKI, acute kidney injury; LUAD, lung adenocarcinoma; BSC, best supportive care.

mechanistic behavior of dd-cfDNA in transplant rejection.

Liver Transplantation

The use of ICIs in liver transplant recipients has been reported mainly in cases of patients with melanoma and cSCC (Table 2). Particularly notable in liver transplantation is the use of ICIs in the treatment of hepatocellular carcinoma (HCC) prior to and subsequent to transplantation. The most common indication for liver transplantation was hepatitis C virus (HCV)-associated cirrhosis at many European and American centers [38,39]. With advances in antiviral agents, the proportion of individuals on the waiting list due to HCV has declined dramatically. Alcohol-associated liver disease and other/unknown diagnoses (often representing liver disease due to non-alcoholic steatohepatitis) are now the leading indications for liver transplant listing. Candidates with a primary diagnosis of HCC compose 10.9% of new waiting list registrations, which has nearly doubled over the past decade in the US [40]. The number of liver transplants for HCC is rapidly increasing, with more than 1,000 liver transplants for HCC performed in the US every year [41]. The indications for transplantation in patients with HCC are based on the Milan criteria, which have been modified to expand the indication metrics over the years [42].

In 2017, the FDA approved nivolumab as an adjunctive treatment for patients whose treatment with sorafenib was unsuccessful. This was followed by the approval of pembrolizumab. The objective response rate (ORR) of nivolumab in patients with advanced HCC previously treated with sorafenib was 15% (CR, 6%; PR, 9%) [43]. The OS was 15% (CR, 6%; PR, 9%), with a median OS of 28.6 months for the first line of treatment and 15.6 months for the second line [44]. The ORR of pembrolizumab was reported as 17% (CR, 1%; PR, 16%) [45]. The options of drug combination therapy for HCC have also expanded, with FDA approval of the combination therapy of ipilimumab and nivolumab for HCC in 2019 [46].

In a recent report, the combination of atezolizumab and bevacizumab prolonged overall and progression-free survival (PFS) compared to sorafenib in patients with unresectable HCC [47]. Moreover, the combination of durvalumab and tremelimumab also significantly improved OS in patients with advanced, unresectable HCC compared to patients who received sorafenib (HIMALAYA study; NCT03298451) [48]. Thus, the combination of ICIs, or ICIs and molecular-targeted therapies is becoming the mainstream for HCC treatment. Accordingly, there has

been an increasing number of case reports of ICI use in patients experiencing posttransplant HCC recurrence. In addition, cases of ICI use before transplant registration and during the waiting period have been reported (Table 2).

Based on a review of the current literature, a total of 42 patients were reported, of which 22 cases were posttransplant and 20 were pretransplant. In the posttransplant cases, rejection was reported in five cases (22.7%). However, six patients (27.3%) showed response to treatment (PR or CR). Among the cases that had received ICI pretransplant, five patients (25.0%) had acute rejection relatively early posttransplant, whereas six patients (30.0%) had a response to treatment (PR or CR). The lower incidence of acute rejection caused by ICIs compared to kidney transplant recipients may be related to the inherent tolerogenicity of liver transplants [49]. Our review identified no cases in which immunotherapy was performed both pre- and posttransplant.

"Liquid biopsy" using circulating tumor DNA (ctDNA) has been demonstrated as an excellent method of minimal residual disease (MRD) surveillance of primary hepatic malignancies in patients who have undergone liver transplants for HCC. ctDNA measures and analyzes DNA fragments derived from tumors that are excreted into the bloodstream. ctDNA provides a non-invasive approach to tracking MRD without the need for repeated tissue biopsies [42]. Ono et al. [50] analyzed ctDNA in 46 patients with HCC, including liver transplant recipients, and found that the cumulative incidence of recurrence and extrahepatic metastasis in the ctDNA-positive group was statistically significantly worse than that in the ctDNA-negative group ($P=0.0102$ and $P=0.0386$, respectively). Multivariate analysis identified ctDNA ($P=0.038$) as an independent predictor of microscopic vascular invasion into the portal vein [50].

Observational studies are also underway to use ctDNA to identify MRD after liver transplant and to correlate the presence of ctDNA with the risk of recurrence [51,52]. Similarly, the usefulness of ctDNA in the setting of ICI therapy has also been reported. A study in which pembrolizumab was used in five different groups of patients with advanced solid tumors showed that both baseline and changes in ctDNA levels from baseline were correlated with OS and PFS [53]. A cohort of 48 patients with unresectable HCC who received atezolizumab and bevacizumab showed that higher baseline ctDNA levels were associated with a greater tumor burden and that dynamic

Table 2. Liver transplantation cases

Study	Type of cancer	Before/after	Allograft outcome	Checkpoint inhibitor	Year from tx to ICI	IS regimen	Cancer response	Interval between IS reduction and ICI initiation	ICI to rejection time
Tsung et al. (2021) [24]	cSCC	After	No rejection	Cemiplimabx2	NA	Tac 1 mg	PD	NA	NA
	cSCC	After	No rejection	Cemiplimabx12	NA	Tac 0.5 mg	NA	NA	NA
Qiu et al. (2020) [55]	HCC Rec	After	No rejection	Camrelizumab	4	Tac → sirolimus	PR	2 yr	NA
Zhuang et al. (2020) [56]	HCC Rec	After	No rejection	Nivolumab	2.7	Tac	SD	NA	NA
Biondani et al. (2018) [57]	LUSC	After	No rejection	Nivolumab	13	Tac+MMF+Pred → Tac+everolimus+Pred	SD	4 yr	NA
DeLeon et al. (2018) [58]	HCC Rec	After	No rejection	Nivolumabx3	2.7	Tac	PD	NA	NA
	Melanoma	After	No rejection	Pembrolizumabx2	5.5	Everolimus, MMF	CR	NA	NA
	HCC Rec	After	No rejection	Nivolumabx4	7.8	Sirolimus, MMF	PD	NA	NA
	HCC Rec	After	No rejection	Nivolumabx5	3.7	Tac	PD	NA	NA
	HCC Rec	After	No rejection	Nivolumabx2	1.2	Tac	NA	NA	NA
	Melanoma	After	Acute rejection	Nivolumabx2	1.1	Sirolimus	NA	NA	27 day
Gassmann et al. (2018) [59]	HCC Rec	After	Acute rejection	Pembrolizumabx2	3.1	MMF, Pred	NA	NA	21 day
Kuo et al. (2018) [60]	Melanoma	After	Cellular rejection	Nivolumab	3	Everolimus	PD	None	7 day
		After	No rejection	Ipilimumab then pembrolizumab	5	Tac+MMF+Pred → sirolimus+MMF	PR	1 yr	NA
Rammohan et al. (2018) [61]	HCC	After	No rejection	Pembrolizumab	3	Tac/sirolimus	CR	NA	NA
De Toni et al. (2017) [62]	HCC Rec	After	No rejection	Nivolumabx15	1	Tac	SD	NA	NA
Friend et al. (2017) [63]	HCC Rec	After	Cellular rejection	Nivolumab	4	Sirolimus 2 mg	NA	NA	17 day
	HCC Rec	After	Cellular rejection	Nivolumab	3	Tac 4 mg	NA	NA	7 day
Schvartsman et al. (2017) [64]	Melanoma	After	No rejection	Pembrolizumab	20	Tac	CR	NA	NA
Varkaris et al. (2017) [65]	HCC Rec	After	No rejection	Pembrolizumab	8	Tac → 50% reduction dose	PD	NA	NA
Morales et al. (2015) [66]	Melanoma	After	No rejection	Ipilimumabx4	8	Sirolimus 3 mg → 1 mg, MMF → off	PR	3 mo	NA
Ranganath et al. (2015) [67]	Melanoma	After	No rejection	Ipilimumab	8	Tac	SD	NA	NA
Chen et al. (2021) [68]	HCC	Before	Acute rejection	Toripalimabx10		Tac, methylprednisolone	PD	None	10 hr
Dehghan et al. (2021) [69]	HCC	Before	Acute rejection	Nivolumab		Tac, MMF, Pred	Near CR	None	POD 10
Qiao et al. (2021) [70]	HCC	Before	Rejection in 1/7	Pembrolizumab or camrelizumab		Tac, MMF, methylprednisolone, Pred, etc.	PR in 71%	None	POD 12 in one case
Tabrizian et al. (2021) [71]	HCC	Before	Rejection in 1/9 (mild, low Tac level)	Nivolumab		Tac, MMF, Pred	Near CR in 3/9	None	NA
Nordness et al. (2020) [72]	HCC	Before	Acute rejection	Nivolumab		Tac, MMF, Pred	CR	None	POD 5
Schwacha-Eipper et al. (2020) [73]	HCC	Before	No rejection	Nivolumab		NA	PR	None	None

tx, transplantation; ICI, immune checkpoint inhibitor; IS, immunosuppressant; cSCC, cutaneous squamous cell carcinoma; NA, not applicable; Tac, tacrolimus; PD, progressive disease; HCC, hepatocellular carcinoma recurrence; Rec, recurrence; PR, partial response; SD, stable disease; LUSC, lung squamous cell carcinoma; MMF, mycophenolate mofetil; Pred, prednisone; CR, complete response; POD, postoperative day.

changes in ctDNA levels after treatment were associated with response. Patients with undetectable ctDNA after treatment had a longer PFS [54]. Based on these results, it is expected that ctDNA will also be introduced as an efficacy indicator for ICI used before and after liver transplantation for HCC. Similar to kidney transplant acute rejection, dd-cfDNA can also be used to evaluate allograft tolerance in liver transplant recipients [74,75]. Levitsky et al. [75] reported that the area under the curve of dd-cfDNA in the acute rejection group (n=57) compared to the normal function group (n=94) was as high as 0.95, and dd-cfDNA decreased alongside normalization after treatment for acute rejection. Therefore, dd-cfDNA may become a biomarker for evaluating rejection in liver transplant patients who receive ICI treatment.

Heart Transplantation

Studies on heart transplant recipients treated with ICIs remain limited. Rejection and myocarditis can be fatal, and therefore more caution is being taken with the administration of ICIs in this patient group. ICI-induced severe myocarditis in non-transplant patients is rare (0.09%) but can be associated with a high rate of mortality [76]. For heart transplant recipients, ICI treatments for melanoma, cSCC, and NSCLC have been reported (Table 3). The mortality attributed to ICI-associated myocarditis, as reported in the World Health Organization database, ranges from 36% to 67% [77]. Alectuzumab (an anti-CD52 antibody) and abatacept (CTLA-4 immunoglobulin) might be effective for treating severe myocarditis. Both alectuzumab and abatacept are potent immunosuppressants used in SOT. Alectuzumab is a monoclonal antibody that binds to CD52, a protein present on the surface of immune cells, such as mature lymphocytes, monocytes, and macrophages, but not on hematopoietic stem cells. Abatacept competes for CD28 occupancy with B7 on APCs, thereby inhibiting the co-stimulatory signaling in T cells [78,79]. ICI-associated rejection is often much more severe than immune-related adverse events in non-transplant patients in general, but these potent immunosuppressants may be able to treat allograft injury caused by ICIs in post-heart transplant patients.

Lung Transplantation

The lung is one of the most immunogenic organs among all SOTs [80], and the recipient requires higher doses of immunosuppressants [81]. As survival improves, the number of patients who develop cancer has been increas-

Case	Type of cancer	Allograft outcome	Checkpoint inhibitor	Year from tx to ICI	IS regimen	Cancer response	Interval between IS reduction and ICI initiation	ICI to rejection time
Daud et al. (2020) [82]	Melanoma	Rejected	Pembrolizumab	18	Tac+azathioprine	NA	NA	Within 3 mo
	LUAC	Rejected	Pembrolizumab	16	CYA, MMF, everolimus/sirolimus, Pred	NA	NA	Within 3 mo
	Melanoma	Rejected	Nivolumab	24	CYA, MMF, Pred	NA	NA	Within 3 mo
	Melanoma	No rejection	Pembrolizumab	19	Tac	NA	NA	
Grant et al. (2018) [83]	Melanoma	No rejection	Pembrolizumab	8	Tac+MMF	PD	NA	
Kittai et al. (2017) [30]	LUSC	No rejection	Nivolumab	10	CYA+MMF+Pred → CYA+MMF	SD	NA	
Owonikoko et al. (2017) [84]	cSCC	Rejected	Nivolumab	19	Tac+sirolimus+Pred → Tac+Pred	NA	NA	5 day
Gastman et al. (2016) [85]	Melanoma	No rejection	Ipilimumabx4	15	Tac+MMF+Pred → Tac+Pred	SD	NA	
Qin et al. (2015) [86]	Melanoma	No rejection	Ipilimumabx4	12	Tac	PD	NA	

Table 3. Heart transplantation cases

tx, transplantation; ICI, immune checkpoint inhibitor; IS, immunosuppressant; Tac, tacrolimus; NA, not applicable; LUAC, lung adenocarcinoma; CYA, cyclosporin A; MMF, mycophenolate mofetil; Pred, prednisone; PD, progressive disease; LUSC, lung squamous cell carcinoma; SD, stable disease; cSCC, cutaneous squamous cell carcinoma.

ing, and potential ICI candidates exist in patients after lung transplants as well. ICI treatment for lung transplant recipients is the least reported among the various types of SOT. This is likely because, as with the heart, severe acute rejection of the lung allograft is directly linked to mortality. In the scope of our review, we found reports of one melanoma case and two cSCC cases treated with ICIs in lung transplant recipients (Table 4). Although acute rejection was not evident in any of the three patients, Tsung et al. [24] reported that the patient developed immune-mediated pneumonitis after two courses of cemiplimab but was discharged home and maintained CR. Daud et al. [82] reported that one of the patients had acute graft dysfunction and the other died within 1 year of ICI treatment due to chronic lung allograft dysfunction. They suggested that ICIs for lung transplant recipients have a higher risk of allograft rejection and/or dysfunction, but might provide therapeutic benefits for their cancer.

RISK FACTORS AND MECHANISTIC INSIGHTS ON ICI-ASSOCIATED REJECTION

The Number of Immunosuppressants in Combination and Steroid Mini-Pulses

Posttransplant cancer is often managed with the reduction or discontinuation of immunosuppressants [87]. Our multi-center study suggested that a higher number of immunosuppressants used in a given patient at the time of ICI initiation was associated with a lower risk of acute rejection. Meanwhile, the ORR to ICIs for both melanoma and cSCC did not differ when stratified by the number of immunosuppressants [15]. Peri-infusion prednisone mini-pulses (40–20 mg over 1–2 weeks, beginning the day of or prior to ICI infusion) followed by 10 mg of prednisone daily for maintenance have also been reported to be effective in the prevention of acute rejection [29,88].

mTOR Inhibitors

mTOR inhibitors have been shown to be effective in cancer prevention and treatment [89]. The TUMORAPA study [90] demonstrated that kidney transplant recipients with a history of cSCC who switched from CNI to sirolimus after the first diagnosis of cSCC had a significant reduction in the recurrence of skin cancer compared to the group that continued CNI. These findings indicate the benefit of mTOR inhibitors in the immune system and for cancer

Table 4. Lung transplantation cases

Case	Type of cancer	Allograft outcome	Checkpoint inhibitor	Year from tx to ICI	IS regimen	Cancer response	Interval between IS reduction and ICI initiation	ICI to event time
Tsung et al. (2021) [24]	cSCC	Immune-mediated pneumonitis (recovered)	Cemiplimabx2	10.8	Tac, Pred 5 mg	CR	NA	After 2 cycles of cemiplimab
Daud et al. (2020) [82]	cSCC Melanoma	Chronic allograft dysfunction	Pembrolizumab	4	Tac, MMF, Pred	NA	NA	
		Acute allograft dysfunction	Ipilimumab	14	Tac, Pred	NA	NA	

tx, transplantation; ICI, immune checkpoint inhibitor; IS, immunosuppressant; cSCC, cutaneous squamous cell carcinoma; Tac, tacrolimus; Pred, prednisone; CR, complete response; NA, not applicable; MMF, mycophenolate mofetil.

control. In the multi-center study described above, the rejection-free graft survival and overall graft survival were both longer in mTOR inhibitor-treated patients than in non-mTOR inhibitor-treated patients with cSCC [15].

Several reports have suggested that mTOR inhibitors may be useful in reducing rejection and controlling cancer [29]. In our multi-center study evaluating ICIs in kidney transplant recipients with cancer, the use of mTOR inhibitors was associated with a lower risk of rejection in multivariate analyses [15]. One case report suggested that sirolimus treatment abated cytotoxic T cell numbers and eosinophilia, while a higher number of Treg cells in the peripheral blood was maintained [91].

Based on the above, Table 5 shows our suggestions on immunosuppression modifications for practical use.

TOLERANCE

Long-term transplant recipients are thought to have established immunological tolerance to some degree and often require fewer immunosuppressants. d'Izarny-Gargas et al. [92] reported that the risk of rejection by ICIs was significantly lower in patients who were more than 8 years posttransplant. They also showed that the use of at least one immunosuppressant in addition to steroids reduced the risk of rejection, while a previous history of rejection significantly increased the likelihood of rejection with ICI treatment.

Table 5. Our recommended potential immunosuppression modifications for practical use

Modification	Detail
Dynamic steroid regimen	Pred 40 mg daily for 3 days (starting from day 1), 20 mg for 3 days, then 10 mg for the rest of the cycle
mTORi conversion	mTORi with a target trough level of 4–6 ng/mL

Pred, prednisone; mTORi, mammalian target of rapamycin inhibitor.

Table 6. Ongoing clinical trials of immunotherapy for cancer in transplant patients

Organ	Study title	Registration	Cancer	Interventions	Phase	Start date
Kidney	Nivolumab in renal transplant recipients with poor prognosis cancers - a safety study [93]	ANZCTR Registration No. ACTRN12617000741381	cSCC, head & neck SCC, melanoma, MCC, NSCLC, urothelial cancer, colorectal cancer, breast cancer, etc.	Nivolumab	I	May 22, 2017
Kidney	Tacrolimus, nivolumab, and ipilimumab in treating kidney transplant recipients with selected unresectable or metastatic cancers [94]	ClinicalTrials.gov Identifier NCT03816332	Melanoma, MCC, BCC, cSCC	Tacrolimus, nivolumab, ipilimumab	I	Feb 1, 2019
Kidney	Cemiplimab in AlloSCT/SOT recipients with cSCC (CONTRAC) [94]	ClinicalTrials.gov Identifier NCT04339062	cSCC	Cemiplimab, everolimus, sirolimus, prednisone	I/II	Jul 15, 2020
Liver	Safety and efficacy of PD-1 inhibitors in patients with liver transplant [94]	ClinicalTrials.gov Identifier NCT03966209	HCC	JS001 (PD-1 inhibitor)	I	May 1, 2019
Liver	Atezolizumab and bevacizumab before surgery for the treatment of resectable liver cancer	ClinicalTrials.gov Identifier NCT04721132	HCC	Atezolizumab, bevacizumab	II	Feb 10, 2021

ANZCTR, Australian New Zealand Clinical Trials Registry; cSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; BCC, basal cell carcinoma; AlloSCT, allogeneic stem cell transplant; SOT, solid-organ transplant; PD-1, programmed cell death protein 1; HCC, hepatocellular carcinoma recurrence.

GENE EXPRESSION ANALYSIS OF ICI-ASSOCIATED REJECTION IN KIDNEY TRANSPLANT RECIPIENTS

ICI-associated acute allograft rejection is histopathologically indistinguishable from other T cell-mediated rejection or acute tubulointerstitial nephritis. Our group recently studied the gene expression signature of kidney biopsies using the Nanostring platform, which enabled us to analyze ~700 immune-related target gene profiles. This study found that the expression level of *IFI27*, an interferon alpha-induced transcript, was higher in cases of T-cell-mediated rejection after ICI use in kidney allograft than in acute interstitial nephritis [95]. Thus biopsy-based measurement of *IFI27* gene expression represents a potential biomarker for distinguishing these entities, and it is expected that a risk assessment based on a genetic diagnosis will be possible through biopsy before treatment.

ONGOING CLINICAL TRIALS

There are five ongoing clinical trials for ICI use in transplant patients: three for kidney and two for liver transplant patients. Table 6 provides an overview of the trials. The first one is “Nivolumab in renal transplant recipients with poor prognosis cancers - a safety study” (ANZCTR registration number ACTRN12617000741381) [93]. This study investigates the safety and efficacy of nivolumab for all types of cancer in kidney transplant recipients. Participants receive nivolumab (3 mg/kg) intravenously every 2 weeks, and the study treatment will continue as long as there is a clinical benefit for up to 2 years. The second study is “Tacrolimus, Nivolumab, and Ipilimumab in Treating Kidney Transplant Recipients With Selected Unresectable or Metastatic Cancers” (NCT03816332), a prospective study comparing existing therapies with tacrolimus, nivolumab, and ipilimumab for treating kidney transplant recipients with advanced melanoma, Merkel cell carcinoma, basal cell carcinoma, and cSCC.

The third is “Cemiplimab in AlloSCT/SOT Recipients with CSCC (CONTRAC)” (NCT04339062), which evaluates the safety and efficacy of cemiplimab as a treatment for advanced cSCC in participants who have previously received a kidney transplant or an allogeneic hematopoietic stem cell transplant. Kidney transplant recipients receive the study treatment drug of cemiplimab along with everolimus, sirolimus, and/or prednisone to prevent kidney re-

jection. The fourth one is “Safety and Efficacy of PD-1 Inhibitors in Patients With Liver Transplant” (NCT03966209), which assesses the safety and efficacy of PD-1 inhibitors such as JS001 in patients with liver transplants. The eligible patients in this study have recurrent or metastatic HCC after liver transplantation and have previously been treated with sorafenib or other targeted therapy. A biopsy is needed to exclude patients with positive allograft PD-L1 expression [94].

The last one is “Atezolizumab and Bevacizumab Before Surgery for the Treatment of Resectable Liver Cancer” (NCT04721132), which is a phase II trial assessing the efficacy of atezolizumab and bevacizumab before surgery in treating patients with liver cancer that can be removed by surgery (hepatectomy or liver transplant). This will be the first international trial that evaluates the utility and safety of atezolizumab and bevacizumab as a bridging therapy to liver transplant for patients beyond the Milan criteria [96]. As the number of cases increases, more clinical studies are anticipated to be conducted to establish a safer and more effective way to use ICIs in transplant recipients.

PATIENT PERSPECTIVES ON POSTTRANSPLANT CANCERS

Cancer is a feared outcome for patients posttransplant. Interviews conducted with 14 post-kidney transplant recipients performed by Williams et al. [97] elucidated patients’ beliefs and attitudes towards posttransplant cancers; patients had limited awareness of posttransplant cancers, and even if they did, it was skin cancer-focused. Patients tended to prioritize their current health issues over cancer screening and prevention, although they felt fear of cancer development. In a larger survey of 1,808 patients posttransplant, the possibility of cancer after transplant was considered to be of critical importance by patients, caregivers, and health professionals [98]. Similarly, a high percentage of recipients have strong hopes for graft survival [99]. These studies highlight the importance of understanding patients’ and caregivers’ values, while demonstrating the necessity of a multi-disciplinary shared decision-making process for cancer treatment options among patients, caregivers, and clinicians. This is particularly important because ICI therapy is associated with a high risk of rejection, and the treatment risk versus

benefit may be perceived differently on a case-by-case basis. To help guide the difficult decision-making, it is crucial to find ways to make ICI treatment more effective and safer for treating transplant recipients with cancer.

CONCLUSIONS

ICI therapy for cancer in transplant patients is still challenging. However, the number of cases is gradually increasing, especially in kidney and liver transplant recipients. The patient populations that can benefit from ICI therapy are gradually becoming clear, depending on the length of time after transplant and the adjustment of immunosuppressants. Prospective studies to better understand the risk factors of rejection and therapeutic targets are underway.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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