Hepatoma Research

Immune checkpoint inhibitors in liver transplant recipients - a review of current literature

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Abstract

Immuno-oncology, particularly with the development of immune checkpoint inhibitors (ICIs), has become a front-line category of cancer-directed therapy, including in the treatment of hepatocellular carcinoma (HCC). While liver transplant (LT) offers a potential cure for HCC, the use of ICIs is a topic of safety concern both pre- and post-transplant due to the risk of donor graft rejection. Nonetheless, some scenarios for which the therapeutic effects of ICI may be highly beneficial include the downstaging of unresectable HCC pre-transplant, or the treatment of recurrent HCC and secondary malignancies post-transplant. In this review, we explored the evidence surrounding the use of ICI in the peri-transplant setting, including safety and efficacy. In a comprehensive review of 28 cases of ICI use post-transplant, we found graft rejection in 9 of 28 cases (32%). Some factors that may increase the risk of rejection include younger age, less time between LT and ICI therapy, and PD-1/PD-L1 expression in the donor graft (particularly when using anti-PD-1/anti-PD-L1 ICIs). Despite these concerns, we relay a case of successful HCC downstaging with nivolumab and subsequent LT. We also describe several cases of response to ICIs post-LT (7 of 28 cases) among a group that is often heavily pre-treated. We conclude that ICIs are valuable options in the peri-transplant setting that have demonstrated promising efficacy based on case reports. Controlled clinical trials are needed to further investigate the conditions that may allow safe delivery of these therapies.

Keywords: Immunotherapy, immune checkpoint inhibitors, CTLA-4 inhibitors, PD-1 inhibitors, hepatocellular carcinoma, liver transplant, allograft rejection

INTRODUCTION

Hepatocellular carcinoma (HCC) is the primary liver tumor and the fourth leading cause of cancer-related death worldwide[1]. Incidence of this disease has steadily increased over the last several years[2]. Established surveillance guidelines have enabled the detection of HCC at an earlier stage. Still, despite these guidelines, a significant number of patients are diagnosed with HCC at an advanced stage when curative therapies are not an option. Systemic chemotherapy using sorafenib was the only standard of care available for patients with advanced HCC for several years; however, multiple alternative agents have now been approved as first line, including lenvatinib. Various second-line therapies have also been approved for HCC; these include several immune checkpoint inhibitors (ICIs), which fall under the broader category of immuno-oncology. While there is an established role for ICIs in advanced disease, there are no clear guidelines or protocols for their use in the peri-transplant setting. There is a higher risk of *de novo* malignancies in liver transplant recipients on immunosuppression. These include skin cancer (with an increased risk of up to 70%); lung, colorectal, and kidney cancers; and recurrent HCC[3]. The role of IO in many of these malignancies is well established in non-transplant patients, but data is limited in solid organ transplant recipients.

The primary concern for the peri-transplant use of ICI is the risk of graft rejection. It is believed that the programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) pathways facilitate immune tolerance of the graft; PD-L1 is expressed in post-transplant liver allografts and PD-1 is heavily expressed on graft-infiltrating T-cells[4,5]. Similarly, binding of CTLA4 on T-cells to its counter-receptor B7 provides an inhibitory signal that terminates T-cell responses[6,7]. Hence, blockade of these pathways may trigger prolific activity of these T-cells, resulting in a T-cell mediated graft rejection. However, based on the limited body of evidence we have reviewed, we hypothesize that there are certain favorable conditions in which ICI use may lend to a decreased chance of graft rejection.

In this review, we will discuss the role of ICI's in the peri-transplant setting, their safety, and their efficacy.

IMMUNE CHECKPOINT INHIBITOR THERAPY PRE-TRANSPLANT

Patients with HCC diagnosed beyond Milan criteria are often treated locoregionally with radiofrequency ablation, transarterial chemoembolization (TACE), or transarterial radioembolization[8]. There is a growing interest in combining systemic with locoregional therapy to downstage these patients and make them eligible for liver transplant (LT)[9]. However, there are limited data on the role of neoadjuvant systemic treatment, including IO in the liver transplant setting. Sorafenib was FDA-approved for treating patients with advanced HCC in 2008, based on a modest improvement in overall survival (OS) compared to placebo (10.7 months *vs*. 7.9 months)[10]. Thereafter, the advanced HCC therapeutic arsenal expanded past sorafenib to include lenvatinib and combined atezolizumab plus bevacizumab as first line therapy and tyrosine kinase inhibitors regorafenib and cabozantinib and ICIs nivolumab and pembrolizumab as second line therapy[11]. However, to date, only sorafenib has been studied in the neoadjuvant setting, but prospective trials have failed to demonstrate any benefit in OS or disease outcome according to RECIST criteria[12,13].

Now that ICIs have a niche in the standard treatment algorithm for advanced HCC[11], there is growing interest in their neoadjuvant use prior to LT. So far, only two case reports have been published in this domain. First, Nordness *et al*.[14] reported a case of poor outcome in a 65-year-old male with HCC within Milan criteria, who quickly failed sorafenib therapy and was initially declined a LT due to up-trending blood alpha fetoprotein (AFP) levels. These levels reached as high as 2500 ng/mL when the patient began treatment with nivolumab (intended as a destination therapy) for almost 2 years before undergoing TACE. This ICI plus TACE strategy maintained the patient's disease within Milan criteria, reducing his AFP levels to 2.3 ng/mL and allowing him to undergo LT 8 days after his last dose of nivolumab. The patient's

postoperative course, which included a standard immunosuppressant drug regimen of tacrolimus, mycophenolate, and prednisone, was unfortunately complicated by signs of profound liver injury on postoperative day (POD) 2. A liver biopsy on POD 6 demonstrated acute hepatic necrosis with profound lymphocyte infiltration, consistent with graft rejection. Despite the initiation of high-dose immunosuppression (methylprednisolone 1000 mg/day and rabbit anti-thymocyte globulin, he expired on POD 10.

In another case reported by Schwacha-Eipper *et al.*[15], a 65-year-old male had a good outcome with neoadjuvant nivolumab followed by LT. He was diagnosed beyond Milan criteria and was started on nivolumab after progression on sorafenib for 14 months. He continued nivolumab for 34 cycles (> 1 year) and had a good partial response with successful downstaging of his cancer, after which he was reevaluated for LT. Due to concern over nivolumab-induced transplant rejection, nivolumab was stopped 6 weeks before listing the patient for transplantation. He was 15 weeks out from his last nivolumab dose when he received a LT. He continues to do well without any evidence of disease recurrence when last reported, one year after surgery.

Given the low sample size, we can only conclude from the two cases reported here that downstaging of HCC for transplant via neoadjuvant IO is feasible in a select population, although the risk of graft rejection poses a real concern. One of the glaring differences between these cases is the timing of the last dose of nivolumab with respect to liver transplantation. A shorter period between the last dose of ICI and LT (8 days *vs.* 15 weeks) may increase the risk of graft rejection. The long-lasting effects of ICIs have been well described. In HCC, pembrolizumab had a median duration of response (DOR) of 13.8 months in KEYNOTE-240, while nivolumab +/- ipilimumab had a median DOR of 17 months in CHECKMATE-040[16-18]. The lasting effects of ICIs are supported by the delayed appearance of adverse events (AEs). The time to onset of ICI AEs varies by organ sites but is generally in the order of weeks to months. For example, the median time to hepatotoxicity is 3 to 9 weeks, and the median time to pneumonitis is about 2.5 months (but may take up to 24 months)[19-21]. Furthermore, nivolumab and pembrolizumab have long half-lives (~25 days)[22]. Usually, it takes 4 to 5 half-lives for plasma concentrations of any given drug to drop below clinically relevant concentrations. We hypothesize that the optimal timing of transplant after the last dose of ICI would be in the order of months, which should take a patient outside of the risk period of the majority of liver-related adverse events, possibly including toxicity to the liver graft. Even so, any lasting effects of ICIs after plasma elimination still need to be determined.

IMMUNE CHECKPOINT INHIBITOR THERAPY POST LIVER TRANSPLANT

Despite increasingly stringent criteria guiding the selection of transplant candidates (i.e., Milan criteria), recurrence of HCC occurs in up to 15%-20% of liver transplant recipients[23-26]. Median survival after recurrence is only around 12 months[25,26]. There is no formal consensus on the appropriate treatment at the time of recurrence. Sorafenib has been commonly used in this scenario, mostly because of concerns related to IO use in a transplant patient on immunosuppressants. However, there is growing interest in exploring IO as a treatment option in this population, especially following the recent ICI approvals for patients with advanced HCC[16,27,28]. Graft recipients are still suspectable to the development of secondary malignancies such as melanoma and lung cancer. In one meta-analysis, investigators found that melanoma was 2.71 times more common in solid organ transplant patients and potentially related to the use of immunosuppressive therapies[29]. Melanoma and lung cancers are now preferably treated with IO[30,31], but, to date, there have been no formal recommendations regarding the use of IO post-transplant, although several case reports document the application of these agents in this setting.

A summary of 28 cases of liver transplant recipients who went on to receive IO is shown in Table 1; this is the most comprehensive list to date[32-50]. HCC was the reason for LT in 22 of these cases. The most common indications for post-transplant IO were recurrent HCC (18 cases) and malignant melanoma (7 cases). Out of all 28 reviewed cases, 4 patients had a confirmed complete response (CR), and 3 had partial responses to IO. Twelve cases had progression of disease after ICI use, and 9 had unknown responses. Specifically, for those with recurrent HCC, 2 of 18 patients had complete responses, and no partial responses were described. Both HCC patients who responded demonstrated durability of these treatment effects, with CR lasting beyond the time of their respective case reports at > 10 months and > 1.5 years. Reportedly, all patients had received at least sorafenib and often had further lines of therapy for HCC prior to receiving IO. As a point of reference, investigators of the Phase II KEYNOTE-224 and phase III KEYNOTE-240 trials described an objective response rate (ORR) in non-transplant HCC patients treated with subsequent-line pembrolizumab of 17% and 18%, respectively[17,27]. Of the 7 melanoma cases shown in Table 1, 2 patients had complete responses, and 2 had partial responses to therapy. When these response data are compared with data from non-transplant patients with advanced melanoma in the Phase III CHECKMATE-066 and KEYNOTE-006 trials, in which nivolumab and pembrolizumab monotherapy were used to treat advanced melanoma, with a ~40% ORR and ~15% CR[51,52], it can be seen that response data are similar. Hence, recurrent HCC or melanoma in liver transplant recipients can respond to IO.

ADVERSE EVENTS

Immune checkpoint inhibitor (ICI) therapy is associated with a spectrum of adverse effects categorized as immune-related adverse events (irAEs)[53]. These toxicities are generally considered distinct from traditional chemotherapy-related adverse effects. The irAEs caused by ICI therapy result from the infiltration of activated T cells into normal tissues. Various organ systems can potentially be affected by ICI treatment; nevertheless, previous ICI trials in HCC have shown these agents to be reasonably well tolerated. Nivolumab demonstrated an acceptable safety profile in Phase I/II and Phase III trials[16,54]. Pembrolizumab has similar safety data[27], as does durvalumab, which is the only anti-PD-L1 monoclonal antibody being studied in HCC, although only Phase I/II trial data is available[55]. It has also been suggested that antitumor response can be enhanced using combinations of drugs with different molecular targets. Thirty-eight percent of HCC patients receiving combined nivolumab plus ipilimumab (anti-CTLA-4 antibody) therapy developed Grade 3/4 treatment-related adverse events. However, only 5% of patients required treatment discontinuation[56]. ICI therapy is now also used in combination with vascular endothelial growth factor A. The recently FDA-approved regimen of atezolizumab plus bevacizumab induced grade 3/4 adverse events in 56% of treated patients, but very few patients required related discontinuation of treatment[28].

Hepatotoxicity is one of the most concerning irAEs related to ICI use. The most common form of liver injury is hepatitis, which is characterized by a marked elevation in aminotransferases with or without an elevation in bilirubin levels. The onset of liver injury is typically within several weeks of therapy initiation. The severity of hepatitis is related to the degree of elevation in aminotransferase and bilirubin levels. The prevalence of hepatic injury related to ICI monotherapy use ranges from 2%-10% in various clinical trials[57]. Significant liver toxicity (Grade 3/4) is rare. However, combination ICI therapy has been associated with higher rates of hepatotoxicity[58], an observation that is likely related to anti-CTLA4 therapy, which reportedly has greater toxicity than PD-1 or PD-L1 inhibitors[59]. Severe hepatotoxicity is typically treated with high dose corticosteroids, and the majority of patients respond well to this treatment[60].

IMMUNOTHERAPY ADVERSE EVENTS IN POST TRANSPLANT PATIENTS
Mechanism of action
The majority of IO safety data are from studies of non-transplant patients; data from patients post-

Table 1. Summary of case reports of use of immune checkpoint inhibitors in the post liver transplant setting

Author	Age (years)	Indication for LT	Indication for IO post-LT	Time from LT to ICI (years)	ICI therapy used	Immune suppression given at time of ICI	Graft PDL1 status	Best response to ICI	Liver toxicity	Time to develop toxicity	Treatment of toxicity	Response to treatment of toxicity
Kumar *et al.*[32] 2019	64	HCC	HCC	2	Nivolumab	NA	NA	NA	**TCMR**	1 week	High dose steroids, ATG, PLEX	Improvement of rejection
Gomez *et al.*[37] 2018	61	HCC	HCC	2	Nivolumab	NA	NA	NA	**TCMR**	1 month	Prednisone	Improvement of rejection
Anugwom *et al.*[38] 2020	62	HCC	HCC	5	Nivolumab	Tacrolimus	NA	NA	Immune hepatitis	2 months	Steroids	Worsening of hepatitis
Varkaris *et al.*[39] 2017	70	HCC	HCC	8	Pembrolizumab	Tacrolimus	NA	POD	no	-	-	-
Friend *et al.*[40] 2017	20	HCC	HCC	3	Nivolumab	Sirolimus	Pos	NA	**TCMR + AMR**	< 1 month	Pulse high dose steroids, IVIG	No response, death
Friend *et al.*[40] *2017*	14	HCC	HCC	2	Nivolumab	Tacrolimus	Pos	NA	**TCMR + AMR**	< 1 month	High dose steroids	No response, death
Rammohan *et al.*[41] 2018	57	HCC	HCC	4	Pembrolizumab + sorafenib	mTOR inhibitor, tacrolimus	NA	CR	No	-	-	-
Amjad *et al.*[42] 2020	62	HCC	HCC	1.3	Nivolumab	Tacrolimus	NA	CR	No	-	-	-
DeLeon *et al.*[43] 2018	56	HCC	HCC	2.7	Nivolumab	Tacrolimus	NA	POD	No	-	-	-
DeLeon *et al.*[43] 2018	55	HCC	HCC	7.8	Nivolumab	MMF, sirolimus	0%	POD	No	-	-	-
DeLeon *et al.*[43] 2018	34	HCC	HCC	3.7	Nivolumab	Tacrolimus	0%	POD	No	-	-	-
DeLeon *et al.*[43] 2018	63	HCC	HCC	1.2	Nivolumab	Tacrolimus	NA	NA	No	-	-	-
DeLeon *et al.*[43] 2018	68	HCC	HCC	1.1	Nivolumab	Sirolimus	30%	POD	**TCMR**	< 1 month	NA	NA (died due to POD)
Gassmann *et al.*[45]	53	HCC	HCC	3	Nivolumab	Everolimus	NA	POD	**TCMR**	2 weeks	Steroids, tacrolimus	No response, death
De Toni *et al.*[46] 2017	41	HCC	HCC	1	Nivolumab	Tacrolimus	NA	POD	No	-	-	-
Al Jarroudi *et al.*[50] 2020	70	HCC	HCC	3	Nivolumab	Tacrolimus	NA	NA	Immune hepatitis ***vs.*** graft rejection	2 months	High-dose steroids	NA
Al Jarroudi *et al.*[50] 2020	62	HCC	HCC	2	Nivolumab	Tacrolimus	NA	POD	No	-	-	-
Al Jarroudi *et al.*[50] 2020	66	HCC	HCC	5	Nivolumab	Tacrolimus	NA	POD	No	-	-	-
Kuo et al.[34] *2018*	62	HCC	Melanoma	4.5	Ipilimumab then pembrolizumab	Sirolimus	NA	PR	No	-	-	-

Schvartzman et al.[35] 2017	35	Biliary atresia	Melanoma	20	Pembrolizumab	Steroids, MMF	NA	CR	Immune hepatitis	1 month	Steroids, MMF	Improvement of hepatitis
Ranganath et al.[36] 2015	59	Cirrhosis	Melanoma	8	Ipilimumab	Tacrolimus	NA	POD	No	-	-	-
Dueland et al.[47] 2017	67	Melanoma	Melanoma	1.5	Ipilimumab	Prednisone	NA	POD	**TCMR**	< 1 month	High-dose steroids, MMF, sirolimus	Improvement of rejection
DeLeon et al.[43] 2018	63	Cholangiocarcinoma	Melanoma	3.1	Pembrolizumab	MMF, prednisone	25%	NA	**TCMR**	< 1 month	ATG, MMF, tacrolimus, prednisone	Improvement of rejection
Morales et al.[44] 2015	67	HCC	Melanoma	8	Ipilimumab	Rapamycin	NA	PR	Immune hepatitis	2 months	None	Improvement of hepatitis
DeLeon et al.[43] 2018	54	HCC	Melanoma	5.5	Pembrolizumab	Everolimus, MMF	0%	CR	No	-	-	-
Chen et al.[33] 2019	61	Cirrhosis	CRC	2.5	Pembrolizumab	Prednisone (1mg/kg), tacrolimus	NA	PR	No	-	-	-
Biondani et al.[48] 2018	54	Cirrhosis	Metastatic Squamous NSCLC	13	Nivolumab	Prednisone, tacrolimus, everolimus	NA	POD	No	-	-	-
Lee et al.[49] 2019	73	HCC	Cutaneous SCC	12	Nivolumab	Everolimus	NA	NA	**TCMR + AMR**	1 month	High-dose steroids, everolimus, MMF	Improvement in TCMR, but persistent AMR

HCC: Hepatocellular carcinoma; CRC: colorectal carcinoma; NSCLC: non-small cell lung cancer; ATG: anti-thymocyte globulin; PLEX: plasma exchange; TCMR: T-cell mediated rejection; AMR: antibody mediated rejection.

transplant are scarce. The mechanism of action of IO agents likely limits their use in the post-transplant setting. It is apparent that the PD-1/PD-L1 and CTLA-4 checkpoint pathways contribute to immune tolerance of a transplanted organ[61]. Immunofluorescence analysis of graft biopsies typically shows high expression of PD-1 and PD-L1 in all graft, highlighting the role of immune checkpoints in graft immune tolerance. Additionally, a mouse orthotopic liver transplant model showed PD-L1 to be expressed by hepatocytes and cholangiocytes of liver allografts, while PD-1 expression was increased on allograft infiltrating T cells[62]. Therefore, it raises concern that administration of ICIs may increase the risk of T-cell mediated rejection (TCMR).

When characterizing graft rejection, we generally consider three subtypes: chronic rejection, antibody-mediated rejection (AMR) and TCMR[4,63]. Graft rejection associated with immunotherapy is an acute process that is believed to T-cell mediated given the loss of immune-tolerance from PD-1/PD-L1 or CTLA-4 pathway blockade. Histological features of cellular rejection include T-cell infiltration and inflammation of the portal, bile duct, and venous endothelial systems[63]. As expected all confirmed cases of graft rejection in Table 1 had at least some component of ACMR, with some AMR.

Of the 28 LT cases shown in Table 1, 7 were tested for PD-L1 status. Four of these 7 cases showed PD-L1 positivity, and all 4 cases (100%) resulted in graft rejection. There is emerging thought around using PD-L1 expression as a marker of safety for anti-PD1 therapy in transplant patients. Mouse models suggest that PD-1/PD-L1 activity, which is a negative costimulatory signal, is necessary for allograft tolerance[64,65]. In pancreatic islet transplantation in mice, PD-L1 deficiency was associated with accelerated graft rejection due to T-cell activation and infiltration. In another small study of 5 solid organ transplant patients, the absence of PD-L1 expression in their respective grafts was used as a marker for anti-PD-1 toripalimab therapy. None of the patients in this study developed graft rejection. From this perspective, a lack of PD-L1 expression in the graft appears beneficial for graft tolerance in the setting of ICI therapy; and in the face of active PD-L1 expression, ICI therapy would jeopardize the graft. Based on this small retrospective study, the PD-L1 status of the allograft may be a useful marker of graft rejection from PD-L1/PD-1 blockade. Therefore, we hypothesize that grafts with a higher baseline level of PD-L1/PD-1 activity would be particularly sensitive to PD-L1/PD-1 inhibition such that the risk of graft rejection is much higher than grafts that are PD-L1/PD-1 negative. This hypothesis calls for investigation and confirmation in a larger study.

Rates of rejection
Even though there is a risk of allograft rejection, IO has been attempted in selected patients post-transplant, as we have outlined above. However, this may come at the cost of an increased risk of graft rejection. A systematic search of 29 patients treated with ICIs following solid organ transplantation by Gassmann *et al.*[45] revealed that graft loss was observed in 36% of orthotopic liver transplant and 54% of kidney graft recipients. The majority of these patients suffered graft loss even on high dose immunosuppression. The predominant ICI used in this series was nivolumab. A larger systematic review of 83 patients published in 2020 by d'Izarny-Gargas *et al.*[66] showed similar results. Allograft rejection was observed in nearly 40% of patients (43% of kidney graft recipients and 37% of liver transplant recipients), and over two-thirds of those patients progressed to end-stage organ failure. Only two patients had a complete recovery on emergency antirejection treatment. The average time to graft rejection from first ICI use was 5.6 weeks, similar to other reported cases in the literature, and alarmingly, the median OS of the 83 patients was a mere 36 weeks. The majority of the patients (73%) were treated with anti-PD-1/PD-L1 inhibitors. In the investigators' multivariate analysis, two factors were associated with a lower risk of rejection: treatment with at least one drug other than corticosteroids for baseline immunosuppression and being at least 8 years out from transplant. Although it is hard to draw a firm conclusion from small uncontrolled trials, the findings reviewed here raise the possibility of using IO safely in patients receiving nonsteroidal antirejection medicines (such as calcineurin inhibitors and mTOR inhibitors).

Of the 28 cases presented in Table 1, there were biopsy-proven acute graft rejections in 9 patients (32%). These patients were generally treated with steroids and often with additional immunosuppression (i.e., tacrolimus, mycophenolate, ATG). This resulted in the resolution of graft rejection in 4 of the 9 cases. Three cases did not improve with immunosuppression and ultimately lead to the patients' demise. One case had an unknown response to immunosuppression. Interestingly, the 3 patients whose graft rejection did not reverse were all younger than 60 years of age (14, 20, and 53), whereas those who recovered from their graft rejection were all over 60 years of age. This pattern of solid organ graft rejection has been seen commonly in liver and kidney transplant cases unrelated to ICI use; hence younger patients have a higher risk of graft rejection, perhaps owing to a more robust immune system[67-69]. It would be reasonable to consider that the use of IO therapy in younger populations may elicit a stronger T-cell mediated response that would more likely jeopardize the graft.

Timing of rejection

As already mentioned, d'Izarny-Gargas *et al.*[66] showed lower rates of rejection in patients who had received a solid organ transplant several years before IO administration. Similarly, in the cases reviewed in Table 1, most graft rejection after ICI therapy occurred in patients who had transplant within 3 years, except one patient with cutaneous SCC who had a rejection from ICI at 12 years post-transplant. Among patients treated with ICI who did not develop rejection, transplant occurred 1 to 20 years from transplant. The median time between LT and ICI therapy was 2 years among patients who had subsequent graft rejection, *vs.* 4.5 years among those who did not. These lower rejection rates when patients are further out from transplant could be due to the development of immune tolerance of the grafted organ; once the early post-transplant period is over, weaker immunosuppression is needed. Thus, the use of ICI may be safer in the late post-transplant period. However, there have been reports of graft rejection with ICI use up to 25 years after transplant[61]. More controlled trials are needed to ascertain the optimal timing of ICI administration in the post-transplant setting.

ICI differences

Anti-CTLA4 therapy has been associated with greater toxicity than PD-1 and PD-L1 inhibitors. However, the degree of anti-CTLA4 agent efficacy and safety post-transplant is particularly unclear due to limited application in this setting. Some case series suggest lower rates of graft rejection with anti-CTLA4 therapy than with PD-1 and PD-L1 therapies. In a small series of published case reports, it was observed that 4 of 10 patients had graft rejection on receipt of PD-1 therapy, whereas 0 of 3 patients treated with anti-CTLA4 ipilimumab experienced graft rejection. There are some data suggesting that the PD-1 pathway plays a larger role in graft immune tolerance, but it is difficult to draw definitive conclusions from these data because of the small and unmatched numbers of patients receiving each treatment type[61]. In a systematic review published in 2020, nivolumab was associated with the highest rate of graft rejection (52%, 12/23), followed by pembrolizumab (26%, 4/15) and ipilimumab (25%, 3/12)[70]. However, these findings were not statistically significant. Although there may be a theoretical basis for anti-CTLA4 therapies being better tolerated from a rejection standpoint, this would have to be explored in further studies.

Treatment and outcomes of rejection

Graft rejection is associated with ICI, even when aggressive immunosuppressant therapy is applied. In their systematic review, Gassmann *et al.*[45] showed the occurrence of end-stage organ failure secondary to rejection in 71% of 29 patients. Another review of 20 patients suggested lower rates of rejection (35%) but a higher mortality rate (38%) in patients experiencing graft rejection[71]. Although these numbers may sound alarming, it is difficult to define the absolute risk of graft rejection associated with ICI in the absence of strict patient selection criteria and randomized controlled trials. The majority of the published data are derived from case reports or series with small sample sizes and likely significant heterogeneity in patient characteristics and treatment, such as patient age, type of immunosuppressant therapy received, number of years out from transplant, and dose and timing of ICI use post-transplant.

FUTURE DIRECTIONS

ICIs appear to demonstrate good anticancer efficacy in the transplant setting but pose a significant risk of graft rejection. The paucity of data generated from ICI use post-transplant - most of which are from individual cases - makes it hard to devise recommendations for their use in this setting. Controlled studies are needed to assess the efficacy and safety of these agents peri-transplant, during which the following should be explored: age of recipient; timing of ICI use in relation to LT; and the use of biomarkers (such as PD-1/PD-L1 expression in the graft) to predict ICI therapy. A sequential series of clinical trials might start with a prospective early phase study to evaluate neoadjuvant IO therapy pre-LT. Patients who have had a response to ICI therapy for HCC (i.e., in the setting of advanced HCC) may be evaluated for LT, and those

who are candidates for LT may be enrolled for transplant in 6 or 12 months following the last dose of ICI. During this period, no further IO therapies is allowed, although bridging therapies (i.e., locoregional therapies) may be employed. This study would help determine a safe duration between IO and LT. Rates of graft rejection would be evaluated as the primary endpoint; secondary endpoints include PFS and OS. If this neoadjuvant approach is shown to be safe, further studies can be considered for post-transplant IO therapy. Once the appropriate patient characteristics are defined, a treatment algorithm may be generated to guide clinicians in the use of ICIs in the peri-transplant setting with the aim of providing effective IO to patients that can and should be allowed to benefit.

DECLARATIONS

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Authors' contributions
Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Yin C, Baba T, He AR, Smith C

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