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MINIREVIEWS

Immunotherapy in liver transplantation for hepatocellular carcinoma: Pros and cons

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Abstract

Liver transplantation (LT) has emerged as a curative strategy for hepatocellular carcinoma (HCC), but contributes to a higher predisposition to HCC recurrence in the immunosuppression context, especially for tumors beyond the Milan criteria. Although immunotherapy has dramatically improved survival for immunocompetent patients and has become the standard of care for a variety of tumors, including HCC, it is mainly used outside the scope of organ transplantation owing to potentially fatal allograft rejection. Nevertheless, accumulative evidence has expanded the therapeutic paradigms of immunotherapy for HCC, from downstaging or bridging management in the pretransplant setting to the salvage or adjuvant strategy in the posttransplant setting. Generally, immunotherapy mainly includes immune checkpoint inhibitors (ICIs), adoptive cell transfer (ACT) and vaccine therapy. ICIs, followed by ACT, have been most investigated in LT, with some promising results. Because of the complex tumor microenvironment and immunoreactivity when immunosuppressants are combined with immunotherapy, it is difficult to reach formulations for immunosuppressant adjustment and the optimal selection of immunotherapy as well as patients. In addition, the absence of effective biomarkers for identifying rejection and tumor response is still an unresolved barrier to successful clinical immunotherapy applications for LT. In this review, we comprehensively summarize the available evidence of immunotherapy used in LT that is specific to HCC. Moreover, we discuss clinically concerning issues regarding the concurrent goals of graft protection and antitumor response.

Key Words: Hepatocellular carcinoma; Liver transplantation; Immunotherapy; Immune checkpoint inhibitors; Adoptive cell transfer; Immunosuppressant

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Core Tip: This review addresses revolutionized immunotherapy for hepatocellular carcinoma (HCC) in liver transplantation (LT), from downstaging or bridging management in the pretransplant setting to adjuvant or salvage strategy in the posttransplant setting. Considering that the benefit of the antitumor response outweighs the incremental risk of rejection, it is worthwhile to take immunotherapy into account as the salvage option when HCC recurs after LT. More prospective studies are required to provide direct evidence regarding immunosuppressant adjustment, biomarkers for response and the optimal selection of immunotherapy as well as patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers, is the fourth leading cause of cancer-related death and is the sixth most commonly diagnosed cancer worldwide[1]. Liver transplantation (LT) is a well-established and highly effective curative therapy for HCC patients with limited tumor burden who are not candidates for resection. However, even for those that meet the strictest Milan criteria based on the explant tumor burden (*i.e.*, a single nodule ≤ 5 cm in diameter or up to three nodules, with none larger than 3 cm in diameter and without tumor invasion into blood vessels or lymph nodes), the risk of HCC recurrence at 5 years after LT is estimated to be 10% to 15%[2]. Moreover, many countries outside the United States adopt expanded criteria rather than the Milan criteria, leading to an even higher incidence of HCC recurrence. When HCC recurs, the fate of the liver transplant recipient may be worse than that of the inoperable patient with advanced HCC, as immune checkpoint inhibitors (ICIs), the most significant breakthrough in recent years in cancer immunotherapy, are used outside the scope of transplantation. Immunotherapy has dramatically improved the survival of immunocompetent patients, with a long-term response and even complete cancer remission, and has become the standard of care for a variety of tumors, including HCC[3]. Immunotherapy, either by reactivating the suppressed intrinsic immune response or by transferring engineered immune cells, is aimed at immunopotentiation to eliminate tumors, which is contrary to immunosuppression for graft protection after transplantation. Therefore, rejection is an inherent risk for liver transplant recipients receiving immunotherapy and presents as a severe pattern that usually progresses rapidly to induce graft loss. In contrast, some patients receive immunotherapy without any sign of rejection, not only in LT but also in other solid organ transplantations. Generally, immunotherapy includes ICIs, adoptive cell transfer (ACT) and vaccine therapy[4]. Currently, most of the published studies on immunotherapy in the setting of LT are related to ICIs, followed by ACT, while vaccine therapy in LT has not been reported thus far. The different types of immunotherapies, as well as different immunosuppressants, have distinct mechanisms of action. When immunotherapy is combined with immunosuppressants in the setting of transplant recipients with malignancies, the interaction among the immune system, graft and cancer is mediated by a much more complex network of biological pathways than any of these entities alone. Many questions regarding the efficacy and safety of immunotherapy in this subgroup of patients remain unanswered. A recent review analyzed 91 patients treated with ICIs after kidney, liver or heart transplantation for different types of cancer and showed that 37 (41%) experienced rejection. Eight (10%) of 80 patients with an available survival status died due to rejection of the transplant, and 41 (51%) died of cancer progression[5]. As cancer progression is a greater threat and because immunotherapy appears to be the last therapeutic option for these patients, it is worth the risk of rejection. In this review, we focus on immunotherapy that is specific to HCC and used perioperatively in liver transplant recipients. We also discuss clinically concerning issues regarding the concurrent goals of graft protection and antitumor response that warrant further investigation.

IMMUNOTHERAPY AS A DOWNSTAGING OR BRIDGING APPROACH TO LT FOR HCC PATIENTS

The American Association for the Study of Liver Diseases suggests that patients beyond the Milan criteria be considered for LT after successful downstaging into the Milan criteria, which has been accepted by the United Network for Organ Sharing and provides a means for making formerly ineligible patients eligible for transplantation. For a long time, ablation and transarterial therapies have been used as two main downstaging approaches as well as bridging approaches, reducing the drop-out risk in the waiting list. Currently, immunotherapy is joining this oncological armamentarium, as an increasing number of clinical trials have shown encouraging objective response rates, even a complete response rate as high as 5.5%[3,4]. To date, 11 reported cases have used immunotherapy before LT (Table 1): 9 in a single-center series and 2 in two separate reports[6-8]. All 11 patients were treated with nivolumab, a programmed cell death protein-1 (PD-1) monoclonal antibody that belongs to ICIs, at a dose of 240 mg every 2 wk. The intra- and posttransplant immunosuppressant regimens were similar. One patient developed acute hepatic necrosis on postoperative day 5 that was likely related to the preoperative use of nivolumab and refractory to high-dose methylprednisolone and rabbit antithymocyte globulin and died on postoperative day 10. Another patient developed acute rejection, probably due to low tacrolimus levels, and responded rapidly to increasing dosages. The native liver explants of 4 patients showed > 90% tumor necrosis. After a follow-up of 16.0 ± 5.8 mo, none of the 10 surviving patients developed tumor recurrence.

Due to the small sample size and selective bias, it was difficult to determine risk factors associated with fatal rejection for those receiving immunotherapy as a downstaging or bridging approach to LT. However, the patient with fatal hepatic necrosis provided some clues. First, he received the longest immunotherapy of nivolumab (nearly 2 years) and underwent LT shortly after the last dose (8 d before transplantation). However, it is worth noting that 3 other patients who received the last dose less than 8 d before LT did not experience rejection, and one even received the last dose 1 d before transplantation with a total duration of 64 wk. However, a short interval between the last dose and LT should be avoided, as the half-life period of nivolumab is approximately 4 wk. Second, pathology of his explant revealed complete tumor necrosis and no evidence of residual HCC. Currently, there are no guidelines proposed for when and how to discontinue or taper ICIs. However, when a patient receiving immunotherapy achieves stable or regressive disease and is listed as a potential candidate for LT, a taper strategy should be considered. Third, the donor of the patient was positive for the HCV antibody, although without active HCV viremia, and there was no evidence of hepatitis or fibrosis on back-table biopsy of the donor liver. The relationship between an HCV-positive donor liver and severe rejection in the setting of immunotherapy needs further investigation.

IMMUNOTHERAPY AS ADJUVANT THERAPY FOR HCC AFTER LT

LT completely removes the primary tumors as well as potential lesions within the diseased liver. Circulating tumor cells or extrahepatic undetected lesions are origins of HCC recurrence. Theoretically, adjuvant therapy after LT can eliminate residual tumor cells, as the tumor burden, if still present, decreases to the lowest level. However, current evidence does not support adjuvant systematic therapies with chemotherapy or sorafenib to reduce the risk of HCC recurrence after LT[9]. A retrospective cohort study of 60 HCC patients within the University of California San Francisco criteria, published in 2018, assessed the posttransplant antirecurrence efficacy of Licardin in single and multiple administrations, a radioisotope iodine (^{131}I)-labeled antibody fragment targeting the HCC-associated antigen HAb18G/CD147, and showed that adjuvant therapy with Licardin significantly reduced HCC recurrence after LT and that multiple administrations had little additional antirecurrence efficacy[10]. However, subsequent studies with larger sample sizes are rare. Due to the unpredictable risk of rejection, which occurs mainly in transplant recipients taking ICIs, immunotherapy as adjuvant therapy after LT should be used cautiously. ACT using natural killer (NK) cells or cytokine-induced killer (CIK) cells seems to be safer than ICIs. Tanimine *et al*[11] reported adjuvant immunotherapy using liver allograft-derived NK cells in 24 HCC patients after living-donor LT at the 2015 American Transplant Congress and stated that the intravenous transfer of processed NK cells to recipients 4 d after LT with a median of 273.5 million cells/patient significantly

Table 1 Characteristics of hepatocellular carcinoma patients receiving immunotherapy as a downstaging or bridging approach to liver transplantation

No.	Ref.	Age	Sex	Underlying liver disease	MTD (cm)	Pathology milan in/out	Cycles/duration	Immunotherapy	Days before LT	Post-LT follow-up (mo)	Initial immunosuppression	Rejection
1	Tabrizian *et al*[6]	69	M	None	10	Milan out within UCSF	21 cycles	Nivolumab	18	23	Tapering steroids + tacrolimus + MMF	No
2	Tabrizian *et al*[6]	56	F	HCV	5.4	Milan out within UCSF	8 cycles	Nivolumab	22	22	Tapering steroids + tacrolimus + MMF	No
3	Tabrizian *et al*[6]	58	M	HBV	21	Milan in	32 cycles	Nivolumab	1	22	Tapering steroids + tacrolimus + MMF	No
4	Tabrizian *et al*[6]	63	M	HCV, HIV	4.4	Milan in	4 cycles	Nivolumab	2	21	Tapering steroids + tacrolimus + MMF	No
5	Tabrizian *et al*[6]	30	M	HBV	3.2	Milan in	25 cycles	Nivolumab	22	16	Tapering steroids + tacrolimus + MMF	Mild
6	Tabrizian *et al*[6]	63	M	HBV	2	Milan in	4 cycles	Nivolumab	13	14	Tapering steroids + tacrolimus + MMF	No
7	Tabrizian *et al*[6]	66	M	HBV	2.5	Milan in	9 cycles	Nivolumab	253	14	Tapering steroids + tacrolimus + MMF	No
8	Tabrizian *et al*[6]	55	F	HBV	2.8	Milan in	12 cycles	Nivolumab	7	8	Tapering steroids + tacrolimus + MMF	No
9	Tabrizian *et al*[6]	53	F	NASH	8.7	Milan out within UCSF	2 cycles	Nivolumab	30	8	Tapering steroids + tacrolimus + MMF	No
10	Schwacha-Eipper *et al*[7]	66	M	Alcohol-associated liver cirrhosis	6.4	Milan out	34 cycles	Nivolumab	105	12	NA	No
11	Nordness *et al*[8]	65	M	HCV	5.5	Milan in	2 yr	Nivolumab	8	Death at day 10	Tacrolimus + MMF + steroids	Yes

M: Male; F: Female; MTD: Max tumor diameter; HBV: Hepatitis B virus; HCV: Hepatitis B virus; UCSF: The University of California San Francisco criteria; LT: Liver transplantation; NASH: Nonalcoholic steatohepatitis; MMF: Mycophenolate mofetil; NA: Not available.

improved the 5-year recurrence-free survival and overall survival rates of patients pathologically exceeding the Milan criteria without any safety issues. Another case report on adjuvant immunotherapy using 5×10^9 CIK cells for 4 cycles one month after LT also showed no severe adverse effects, including rejection[12]. If we can distinguish patients with a low risk of rejection, immunotherapy, especially with ICIs, will be a very promising adjuvant therapy for those at a high risk of HCC recurrence after LT because of its superior performance on tumor response compared with other systemic therapies.

IMMUNOTHERAPY FOR HCC RECURRENCE AFTER LT

As described previously, HCC patients after LT are exposed to an inevitable risk of HCC recurrence, and unfortunately, there is a limited therapeutic arsenal available for the HCC recurrence subpopulation with progressive disease (PD) after routine treatment failure. However, in more recent years, growing research on immunotherapeutic applications in the transplant setting has yielded promising results that have revolutionized the therapeutic landscape of cancer recurrence after transplantation. Thus far, the cumulative literature on transplant immunotherapy is primarily focused on kidney transplantation[5]. A multicenter retrospective study covering 69 kidney transplant patients receiving ICIs reported improved overall survival (OS) despite a

concomitant increased risk of rejection[13]. Given the satisfactory clinical outcomes, mounting research has been conducted to explore the potential of immunotherapy in liver transplant recipients with recurrence or *de novo* malignancy. Various malignancies can occur after LT, and melanoma patients seem to exhibit a favorable tumor response to immunotherapy and acceptable rejection rate[14-16]. In a review of ICIs for 6 melanoma patients after LT, 2 achieved complete remission (CR), 2 achieved partial remission (PR), and the remaining 2 developed PD; of note, no patient experienced allograft rejection[14]. There are also emerging reports on HCC recurrence treated with immunotherapy after LT (Table 2). To our knowledge, 29 patients with HCC recurrence had received immunotherapy after LT: 19 received ICIs [PD-1 inhibitors in 15 patients and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitor in 4 patients], and 10 received cell-based immunotherapy [9 based on T cell receptor (TCR) T cells and one based on allogenic NK cells]. The median patient age was 56 (14-70) years, and 78% of patients were male. Among the patients with recurrence sites reported, patients who developed intrahepatic HCC recurrence alone after LT accounted for 11% (2/18), those who developed extrahepatic recurrence alone accounted for 56% (10/18), and those who developed both accounted for 33% (6/18). The estimation of the efficacy and safety of immunotherapy was performed based on the summarized data (Table 2).

Efficacy: The last chance for liver transplant recipients who develop HCC recurrence

Multiple treatments were used before the initiation of immunotherapy, including sorafenib (n = 14), regorafenib (n = 5), lenvatinib (n = 2), chemotherapy (n = 7), radiotherapy (n = 5), transarterial chemoembolization (n = 4), ablation (n = 3) and surgery (n = 1), and all failed to control the disease. Therefore, salvage immunotherapy has been increasingly utilized as the last option for such subpopulations. Excluding patients whose responses were not reported or could not be assessed because of rapid progression to death or immunotherapy discontinuance after rejection, a total of 16 (55.2%) patients were eligible for response evaluation. The overall response rate (ORR) (CR + PR) was 31.3% (5/16) [including 18.8% (3/16) with CR and 12.5% (2/16) with PR], although 68.8% (11/16) of patients failed to respond to immunotherapy. In the ICI subgroup, the ORR was 25% (3/12), which manifested a numerically improved antitumor response in transplant patients compared to that in nontransplant patients with advanced HCC, where the ORRs to nivolumab and pembrolizumab were 15% and 18.3%, respectively[17,18]. Such a difference was difficult to interpret in terms of clinical benefit due to the limited sample size and selection bias, so further studies are necessary to establish whether each individual immunotherapy agent plays a different role through a specific mechanism in the liver transplant setting. For a single immunotherapy agent, the tumor response rates of patients treated with nivolumab, pembrolizumab, and ipilimumab were 11% (1/9), 50% (1/2), and 100% (1/1), respectively. This is discordant with a previously reported review across multiple organ transplantations, where the tumor response rates were 31% (8/26), 48% (12/25), and 29% (4/14), respectively[5].

On the other hand, 9 patients, all from a consecutive cohort led by researchers in Singapore, were treated with HBV-specific TCR T cells[19-21]. Three patients were reported to have a response, one achieved PR with a follow-up of 1 year, and two had PD. Furthermore, HBV-specific TCR T cells were engineered by researchers using the electroporation technique to gain short-term immunosuppressant resistance, which would be very promising in the setting of LT[19]. Another patient who achieved PR was an isolated case with a follow-up of 18 mo; in this patient, allogenic NK cells combined with iodine-125 seed implantation were used[22]. Whether NK cell transfer plays a dominant role in this combined immune-radiotherapy should be investigated through further studies.

In general, considering that the promising antitumor response outweighs the incremental risk of rejection when immunotherapy is used as a non-first-line protocol for liver transplant recipients who develop HCC recurrence, it is worthwhile to take immunotherapy into account as the last salvage option.

Safety: Rejection can be fatal, while PD inevitably leads to death

Because of the advanced stage of HCC when immunotherapy was administered, PD, which rapidly led to death, was the most common response status (12/16). The median duration of immunotherapy was 8.6 wk (IQR 4, 23 wk) and was not long enough to fully expose other immunotherapy-related adverse effects (irAEs) apart from rejection, which might also be related to immunosuppressant usage. Four

Table 2 Characteristics and reported outcomes of published cases with hepatocellular carcinoma recurrence receiving immunotherapy after liver transplantation

No.	Ref.	Age	Sex	HCC recurrence	Immunosuppression protocol before immunotherapy	Compound	Duration of IMT (wk)	Interval from LT to IMT (yr)	Graft rejection	Tumor response	Follow-up (mo)	Cause of death
1	De Toni and Gerbes [27]	41	M	IR and ER	Low-dose tacrolimus	Nivolumab	30	1	No	PD	10	-
2	Friend *et al* [59]	20	M	ER	Sirolimus	Nivolumab	4	4	Yes, lethal (17 d)	NA	1	OF (4 wk after ICI initiation)
3	Friend *et al* [59]	14	M	ER	Tacrolimus	Nivolumab	2	3	Yes, lethal (7 d)	NA	1	OF (5 wk after ICI initiation)
4	Varkaris *et al*[25]	70	M	ER	Low-dose tacrolimus	Pembrolizumab	11.3	8	No	PD	3	PD
5	DeLeon *et al*[60]	57	M	HCC recurrence	Tacrolimus	Nivolumab	5.1	2.7	No	PD	1.2	Probably PD
6	DeLeon *et al*[60]	56	M	HCC recurrence	Sirolimus + MMF	Nivolumab	4.7	7.8	No	PD	1.1	Probably PD
7	DeLeon *et al*[60]	35	F	HCC recurrence	Tacrolimus	Nivolumab	5.6	3.7	No	PD	1.3	Probably PD
8	DeLeon *et al*[60]	64	M	HCC recurrence	Tacrolimus	Nivolumab	1.3	1.2	No	NA	0.3	MOF
9	DeLeon *et al*[60]	68	M	HCC recurrence	Sirolimus	Nivolumab	3.9	1.1	Yes (27 d)	NA	0.9	PD
10	Gassmann *et al*[58]	53	F	ER	Everolimus + MMF + steroids	Nivolumab	2	3	Yes, lethal (7 d)	NA	0.8	OF (2 wk after ICI initiation)
11	Rammohan *et al*[32]	57	M	ER	Tacrolimus + MMF + steroid + mTOR inhibitor	Pembrolizumab	42.9	4.3	No	CR	10	Alive
12	Zhuang *et al*[90]	54	M	ER	Tacrolimus	Nivolumab	62	2.7	No	PD	20	PD
13	Al Jarroudi *et al*[91]	70	M	IR	Tacrolimus	Nivolumab	8	> 3.0	Yes (45 d)	NA	4	PD
14	Al Jarroudi *et al*[91]	62	F	ER	Tacrolimus	Nivolumab	10	2.5	No	PD	2.5	Alive
15	Al Jarroudi *et al*[91]	66	M	IR and ER	Tacrolimus	Nivolumab	12	> 4.75	No	PD	3	Alive
16	Amjad *et al* [24]	62	F	IR and ER	-	Nivolumab	82.7	1.3	No	CR	20	Alive
17	Wang *et al* [92]	48	M	ER	Sirolimus + tacrolimus	Pembrolizumab	3	1	Yes (5 d)	NA	8	Alive
18	Qiu *et al* [93]	54	M	IR and ER	Sirolimus	Camrelizumab	39	4.3	No	PD	11	PD
19	Tan *et al* [21]	56	M	ER	Tacrolimus + MMF	HBV-TCR T cells	52	1.1	No	PR	12	Alive
20	Tan *et al* [21]	45	M	IR and ER	Sirolimus	HBV-TCR T cells	16	4.4	No	PD	3.7	Alive
21	Qasim *et al* [20]	70	M	ER	Tacrolimus	HBV-TCR T cells	8.6	11	No	PD	2	PD
22	Hafezi *et al* [19]	-	-	HCC recurrence	Tacrolimus + sirolimus	HBV-TCR T cells	10	1.5	-	-	-	-
23	Hafezi *et al*	-	-	HCC	Tacrolimus + sirolimus	HBV-TCR T	4	1	-	-	-	-

	[19]			recurrence	+ MMF	cells						
24	Hafezi *et al* [19]	-	-	HCC recurrence	Tacrolimus + sirolimus	HBV-TCR T cells	9	1.8	-	-	-	-
25	Hafezi *et al* [19]	-	-	HCC recurrence	Tacrolimus + MMF	HBV-TCR T cells	4	0.4	-	-	-	-
26	Hafezi *et al* [19]	-	-	HCC recurrence	Sirolimus	HBV-TCR T cells	4	0.5	-	-	-	-
27	Hafezi *et al* [19]	-	-	HCC recurrence	Tacrolimus + sirolimus	HBV-TCR T cells	8	0.7	-	-	-	-
28	Xie *et al*[22]	29	M	IR	-	NK cells	12.9	1.5	No	PR	18	Alive
29	Pandey and Cohen [49]	54	F	IR and ER	Tacrolimus	Ipilimumab	55.7	7.5	No	CR	27	Alive

M: Male; F: Female; IMT: Immunotherapy; IR: Intrahepatic recurrence; ER: Extrahepatic recurrence; MMF: Mycophenolate mofetil; CR: Complete response/remission; PR: Partial response/remission; PD: Disease progression/progressive disease; NA: Not available; OF: Organ failure; MOF: Multiple organ failure.

patients developed grade 1-2 transaminitis, two patients developed a biliary stricture that needed stent implantation, and one patient experienced chills, fatigue, and fever. In the ICI immunotherapy subgroups, survival status was determined for 19 patients, and 32% (6/19), including 5 receiving nivolumab and 1 receiving pembrolizumab, experienced rejection. Interestingly, patients who developed both intra- and extrahepatic recurrence appeared to have a lower predisposition to rejection than those who developed intra- or extrahepatic recurrence alone; the incidence of rejection was 0% (0/5), 100% (1/1), and 50% (4/8), respectively. Allograft rejection exhibited a tendency to occur shortly after immunotherapy initiation, at a median time of 12 d (range 5-45 d). No difference in the interval from LT to ICI initiation was detected between patients who did and did not experience rejection (P = 0.191). The mean interval was 2.5 ± 1.2 years for those who experienced rejection and 4.0 ± 2.5 years for those who did not. Although statistical significance was not achieved, perhaps partially due to limited data, patients with a short interval seemed to be at a higher risk of rejection than those with a long interval. After a median follow-up of 3 (0.3-27) months, 68% (13/19) of patients died, but only 23% (3/13) of deaths were attributed to immediate rejection. This result was consistent with the preexisting literature on immunotherapy across multiple solid organ transplantation, which demonstrated that rejection-specific mortality was far less frequent than cancer-specific mortality (23% *vs* 77% in our pooled analysis)[5]. In addition, the graft rejection rates of patients treated with nivolumab, pembrolizumab, and ipilimumab were 36% (5/14), 33% (1/3), and 0% (0/1), respectively. In a systematic review of ICIs for organ transplant patients with a variety of cancers published in 2020[23], among all transplant recipients, the graft rejection rates of patients treated with nivolumab, pembrolizumab, and ipilimumab were 54.2%, 44% and 23%, respectively, and among all liver transplant recipients, the graft rejection rates were 33%, 25% and 12.8%, respectively. This tendency is consistent with our pooled analysis, which indicates that PD-1 inhibitors contribute to a higher risk of graft rejection than CTLA-4 inhibitors. Of note, one patient who experienced two episodes of acute cellular rejection before immunotherapy did not experience rejection after immunotherapy, which revealed that a history of rejection might not be a contraindication for immunotherapy[24].

In the cell-based immunotherapy subgroups, 10 patients received immune cell infusion, and 4 had evaluable graft rejection information. Notably, all 4 patients were successfully infused without severe irAEs or allograft rejection at a median duration of 10.8 wk (range 8.6-52 wk), which suggests that ACT might be superior to ICIs in terms of safety profile. Additionally, intensified immunosuppressive regimens were not applied during the ACT infusion, and tacrolimus-based immunosuppressive regimens accounted for 80% (8/10). Minimal but therapeutic immunosuppressive protocols merit further exploration for ACT immunotherapy.

Taken together, these results suggest that although allograft rejection can be fatal, the relatively low risk of rejection-associated death warrants consideration of immunotherapy as an alternative strategy because disease progression inevitably leads to death.

HOW TO BALANCE GRAFT-PROTECTIVE IMMUNOSUPPRESSION AND ANTITUMOR IMMUNOPOTENTIATION

Lifelong immunosuppression is required for liver transplant recipients to maintain graft protection. However, immunosuppressants might exert adverse pressure on the antitumor efficacy of immunotherapy by dampening host immune capacity[25,26]. According to the currently available data, favorable immunological and oncological responses are still obtained, even noninferior to those in the nontransplant setting, which suggests an incompletely antagonistic relationship between immunosuppression and the antitumor efficacy of immunotherapy. Nevertheless, on the one hand, conventional immunosuppressant regimens for liver recipients receiving immunotherapy may lead to neither graft rejection nor significant antitumor efficacy[27]. On the other hand, the usage of immunotherapy recommended for nontransplant HCC patients might not be fully applicable for liver transplant recipients who develop HCC recurrence. Therefore, how to balance graft-protective immunosuppression and antitumor immunopotentiation remains a critical issue, and further comprehensive investigations are required to explore individual usage and mechanisms in the simultaneous utilization of immunosuppression and immunotherapy.

Adjustment of the immunosuppressant regimen

The immunosuppressive microenvironment plays an important role in immune tolerance and graft protection. Currently, the major immunosuppressants used for liver recipients include calcineurin inhibitors (CNIs), steroids, antimetabolites, and mammalian target of rapamycin (mTOR) inhibitors, which inhibit T cell activation by blocking signaling pathways (signal 1: Antigen presentation and recognition, HLA-TCR/CD3, signal 2: Costimulatory signaling, and signal 3 cytokine priming)[28]. The major clinical immunosuppressants target signals 1 and 3, while cancer immunotherapy targets signal 2[29]. CNIs, such as FK506, which targets signal 1, partially block IL-2 expression by disrupting the activation of nuclear factor of activated T cells [28,30]. Due to the unquestionable capacity of rejection reduction, CNIs are extensively used for the majority of liver transplant recipients[31]. In our pooled analysis, 70% (19/27) of patients were administered a tacrolimus-based immunosuppression protocol during immunotherapy, and 3 achieved a tumor response (2 CRs and 1 PR). Of concern is that low-dose tacrolimus, the minimal immunosuppression strategy, does not increase the burden of rejection and concomitantly avoids interference with the antitumor immune activity of immunotherapy[25,27,32]. Different from CNIs, mTOR inhibitors, including sirolimus and everolimus, block signal 3 of final T cell activation by inhibiting the cell cycle transition from G1 to S phase and thereby influence both the proliferation and activation of T lymphocytes[33,34]. Additionally, mTOR inhibitors have antitumor properties, and as a result, mTOR inhibitors are inclined to be used for liver transplant patients with HCC[35]. However, whether mTOR inhibitors play an essential biological role in graft protection and antitumor efficacy for liver transplant patients who develop HCC recurrence remains unclear. More recently, two studies tended to support the notion that mTOR inhibitors had the potential to uncouple the efficacy and rejection of ICIs in renal transplantation[13,36]. Compared to non-mTOR inhibitor subsets, the administration of mTOR inhibitors in renal transplant patients with malignancy presented a lower predisposition to rejection and simultaneously resulted in improved rejection-free graft survival and overall graft survival[13]. Apart from the aforementioned immunosuppressants, an increasing number of immunosuppressants appear to be associated with a low risk of rejection without affecting the ORR of the tumor to ICIs. Therefore, based on preliminary evidence, regimens combining mTOR inhibitors with low-dose tacrolimus may warrant consideration as an alternative strategy.

Moreover, whether additional steroids may antagonize the therapeutic profile of immunotherapy also remains controversial. Murakami *et al*[13] reported that steroids can diminish the effect of immunotherapy. Conversely, some studies of immunotherapy for organ transplant patients indicated that additional steroids may not exert a negative effect on the efficacy of immunotherapy and may even decrease the risk of irAEs[32,37]. A systematic review involving 39 allograft transplant patients treated with ICIs revealed that individual immunosuppressive regimens had different effects on allograft rejection and tumor response[38]. The allograft rejection rates with a single agent, including prednisone, mTOR inhibitors, or CNIs, and the combination regimen were 78% (7/9), 67% (2/3), 11% (1/9), and 29% (5/17), respectively. The tumor response rates to ICIs were 63% (5/8), 50% (1/2), 25% (2/8), and 50% (7/14)[38]. It is presumed that a single steroid regimen may be insufficient to prevent rejection,

despite a satisfactory tumor response. Thus, steroids combined with other low-dose immunosuppressants, such as CNIs and mTOR inhibitors, may yield promising outcomes in specifically stratified subgroups. Nevertheless, there is no definitive conclusion on the respective contributions of immunosuppressants in HCC patients after LT in our pooled analysis due to the absence of supporting information. Taken together, these findings indicate that given the limitation and heterogeneity of the experimental data, the optimal immunosuppressant regimen cannot be determined, and a combined strategy of mTOR inhibitors and low-dose tacrolimus, with or without steroids, warrants further validation.

Choice of immunotherapy and whether use it in a modified manner

The antitumor efficacy and rejection risk of each individual immunotherapy are distinctly different, and the identification of specific patients and selection of a reasonable management plan based on the respective biological properties of each immunotherapy are urgent matters. The most clinically relevant inhibitory costimulatory pathways (signal 2) are the PD-1:PD-L1/PD-L2 and CTLA-4/B7 axes, which are considered to function at different phases of the T cell response. Both of these inhibitory pathways contribute to immune tolerance; in addition, the PD-1 axis is thought to be the most essential for graft tolerance primarily during the maintenance phase across the posttransplant process, while the CTLA-4/B7 axis functions during the induction phase[39-41]. Therefore, PD-1 inhibitors (nivolumab, pembrolizumab) are more likely to give rise to graft rejection than CTLA-4 inhibitors (ipilimumab), as delineated in our analysis and a previous review[23]. Given that the CTLA-4 axis functions during the induction phase of immune tolerance, some studies have reported that CTLA-4 blockade at the late stage resulted in a lower risk of rejection than that at the early stage[23,42,43]. From the scant evidence, CTLA-4 inhibitors (ipilimumab) are likely more appropriate than PD-1 inhibitors for patients at a high risk of rejection or with a remote LT history.

PD-L2, unlike PD-L1 (the major ligand for PD-1 in peripheral tissues), is more commonly expressed on monocytes and dendritic cells than on tumor cells, and both PD-L1 and PD-L2 are considered to play crucial roles in allograft tolerance[44]. Therefore, from the clinical perspective, PD-L1-specific blockade (preventing the binding of PD-L1 to PD-1) may contribute to a lower predisposition to allograft rejection than PD-1 blockade (preventing the interactions of PD-1 with PD-L1 and PD-L2), partially owing to the preserved biological effects of the PD1/PD-L2 axis in immune tolerance. However, the therapeutic differences in activity and toxicity between PD-1 inhibitors and PD-L2 inhibitors remain to be further evaluated.

To date, no solid conclusion has been drawn regarding whether a modified method is required for immunotherapy. All patients with available information in our analysis were administered ICI immunotherapy in accordance with the instructions. From the perspective of the dose-effect relationship, low-dose exposure to nivolumab (≥ 0.3 mg/kg) could competitively saturate peripheral receptor occupancy and contribute to comparable antitumor efficacy[45,46]. In particular, low- but therapeutic-dose immunotherapy may not only relatively reduce adverse events and financial burden but also not compromise efficacy. Further prospective investigations are needed to explore the precise dose-effect relationship of each individual agent in HCC patients undergoing LT.

Notably, given that the efficacy of ICIs usually appears within 3 mo after initiation [47] and that PD-1 receptor occupancy lasts up to 85 d[48], a markedly prolonged duration is inadvisable because of the increased risk of rejection. Nordness *et al*[8] reported a case in which a recipient who received nivolumab for 2 years prior to LT developed fatal rejection, but pathology of his explants revealed complete tumor necrosis and no evidence of residual HCC. In another published case report, a partial tumor response occurred after three doses of ipilimumab (3 mg/kg), and CR was eventually achieved following the fourth dose of a 3-wk schedule conversion to a 12-wk schedule; notably, a durable response of 27 mo was obtained after a 13-mo ipilimumab regimen[49]. In view of the above results, a tumor response may develop at a relatively early stage, and a prolonged duration of immunotherapy would lead to immunotherapy resistance or severe adverse events. As a result, a prolonged cycle interval and even withdrawal need to be taken into consideration after a definitely complete tumor response based on periodic evaluations and timely identification.

Currently, the exploited cell subgroups of ACT mainly include tumor-infiltrating lymphocytes (TILs), CIK cells, lymphokine-activated killer cells, NK cells, T cells, and genetically redirected cells. In several accomplished studies, chimeric antigen receptor (CAR) T cell immunotherapy targeting tumor-associated antigens (TAAs) showed strong antitumor capacities but also nonnegligible adverse events, such as cytokine

release syndrome (CRS) and neurotoxicity, which limited its clinical applications in the liver transplant setting[50,51]. Unlike CAR-T cell therapy, CAR-NK cell therapy rarely elicits CRS or neurotoxicity; thus, CAR-NK cell therapy might be more suitable for translation into organ transplantation[52]. In our pooled data, CIK cells, NK cells, and HBV-TCR T cells were used in a liver transplant setting with promising clinical results. However, there are many unsolved problems regarding highly efficient production, dosing adjustment, and identification of tumor-specific antigens. Based on existing experiences, dose escalation and a relatively low-dose regimen might be favorable in the liver transplant setting. Considering the high heterogeneity of HCC, engineered cells with multiple targets and combined regimens represent new frontiers.

As mentioned above, there is still no study reporting vaccine therapy in the setting of LT. Even in a nontransplant setting, only a few trials of vaccine therapy targeting HCC-associated antigens have been performed, and none of them has provided clinically meaningful results. However, a strategy using neoantigens has emerged as a promising approach to develop cancer vaccines with intense tumor-specific nontoxic responses due to advancements in the field of high-throughput screening. The ability to predict highly immunogenic neoantigens with antitumor activity as vaccines using this approach has been shown in melanoma[53] and glioblastoma[54]. Although vaccines are traditionally considered a stand-alone therapy, there is a tendency to combine them with ICIs or ACT.

Surveillance and management of immunotherapy-related rejection

Immunotherapy-related rejection remains the major barrier to clinical immunotherapy promotion in HCC patients after LT. For liver transplant recipients receiving immunotherapy, the identification of rejection is easily confounded by immune-related hepatitis, a kind of irAE, which is characterized mainly by mild transaminitis (grades 1-2)[55]. Thus, caution is strongly warranted to distinguish immune-related hepatitis and rejection when apparent liver malfunction is detected. Compared with rejection, hepatitis occurs at a later stage following immunotherapy initiation (median time, 22 d *vs* 5-6 wk)[5,55] and rarely leads to fatal outcomes. Beyond this, immune-related hepatitis is more common in patients treated with CTLA-4 inhibitors[56], whereas allograft rejection is more frequently recorded in liver transplant patients treated with PD-1 inhibitors[23]. When a definite diagnosis cannot be made by virtue of the information above, graft biopsy should be performed and evaluated based on the Banff schema[57]. Generally, immune-related hepatitis is primarily characterized by acute lobular hepatitis, whereas allograft rejection is predominantly characterized by portal inflammation, bile duct damage, and endotheliitis[58]. Clinically, hepatitis and rejection do not seem to be completely distinct, and to some extent, they could be partially homologous. If a single liver biopsy presents both pathological features simultaneously, it is difficult to identify potential mutual interactions involved in disease progression; therefore, given the potential benefit for rejection control, further studies are required to explore the underlying relationship of hepatitis and rejection.

In particular, surveillance should focus on stratified populations who tend to be susceptible to rejection. Although no difference was detected in the interval from LT to ICI initiation between patients who did and did not experience rejection (2.5 ± 1.2 years *vs* 4.0 ± 2.5 years, $P = 0.191$), patients with a narrow interval from LT to immunotherapy initiation exhibited a tendency to have a higher risk of rejection. Moreover, in our analysis, rejection usually occurred shortly after immunotherapy initiation, at a median time of 12 d (range 5-45 d) or at a short cycle (range 1-4 cycles); therefore, more intensive surveillance is recommended during the early period after immunotherapy initiation. Of concern, PD-L1 expression on graft lymphocytes was reported to be strongly associated with rejection after ICI initiation[59,60]; however, Nordness *et al*[8] reported a case of rejection whose PD-L1 staining appeared to be negative before transplantation but positive after transplantation. It can be speculated that PD-L1 expression manifests as a secondary phenomenon following rejection, and therefore, liver biopsy should be performed routinely to validate its predictive efficacy.

Since allograft rejection largely appears to be life-threatening, effective preventive and therapeutic interventions are critically required in clinical practice. Evidence indicates that a cellular-mediated mechanism plays a key role in graft rejection, whereas an antibody-mediated mechanism is secondary only to the former[61,62]. In accordance with this evidence, all 3 evaluable patients enrolled in our analysis experienced cellular-mediated rejection, and 2 experienced both cellular- and antibody-mediated rejection. Typically, in liver transplant recipients who do not receive ICI treatment, approximately 75% of acute cell-mediated rejection can be mitigated with high-dose steroids[58,63]. Comparatively, in this population taking ICIs, only 29% of patients with allograft rejection were salvaged throughout the

treatment course; most patients experienced graft failure[23]. This is consistent with our analysis, where only 2 of 6 (33%) recipients showed a response to steroids. Furthermore, dialysis is often used as an alternative option for rejection in renal transplant recipients, but whether it is feasible in liver transplant recipients remains unclear[38]. Some scholars recommend plasmapheresis as a viable alternative solution for immunotherapy-induced rejection. Although plasmapheresis is mainly thought to alleviate acute antibody-mediated rejection rather than cell-mediated rejection, it can substantially accelerate clearance from the circulation and thus mitigate immunotherapy-induced rejection[58,64]. In addition, antithymocyte globulin and infliximab were reported to be successfully used for acute rejection in liver transplant recipients, but further investigation is needed[65,66]. In summary, an in-depth collaboration involving the patient, surgeon, and oncologist is urgently necessary to identify individualized risk-benefit profiles because of the absence of highly effective therapeutic means available.

Immunotherapy combined with other treatments

To achieve a higher response rate, combination strategies based on immunotherapy might be a promising direction toward optimal antitumor efficacy in liver transplant recipients who develop HCC recurrence. Combination with conventional HCC therapies is the first option. Locoregional liver-directed therapies, such as ablation and transarterial therapies, exhibit the dual effects of robust tumor destruction to liberate substantial TAAs and strongly activate the immune response by priming tumor-specific T cells[67]. Such therapy-induced immunogenic modulation of tumors might amplify the antitumor efficacy of CD8+ effector T cells activated by ICIs[67].

In addition, molecularly targeted therapies with immunotherapies have become the standard of care for advanced HCC. The FDA, EMA and other regulatory agencies worldwide have approved the PD-L1 inhibitor atezolizumab plus vascular endothelial growth factor (VEGF) inhibitor for first-line therapy in HCC. Atezolizumab plus bevacizumab is now listed as the preferred regimen in first-line systemic therapies by National Comprehensive Cancer Network guidelines for HCC, replacing sorafenib and lenvatinib[68,69]. The combination with lenvatinib was associated with double the response rate compared with that observed with single-agent pembrolizumab, but this came at the cost of increased toxicity[70]. In addition, tyrosine kinase inhibitors (TKIs), such as sorafenib, regorafenib and lenvatinib, have been shown to have immune-associated antitumor capacity independent of anti-VEGFR mechanisms[71]. Accumulative studies have demonstrated that sorafenib can stimulate antitumor efficacy by strengthening CD4+ and CD8+ T cell function and infiltration and inhibiting T-reg cells[72-74]. In the liver transplant setting, it has been reported that an HCC patient following LT developed metastatic lung lesions and subsequently received sorafenib but experienced disease progression after 1 year. Then, pembrolizumab was added to sorafenib treatment, and ultimately, the patient achieved CR without allograft rejection[32], which indicated the crucial synergistic antitumor efficacy of the combination of PD-1 inhibitors with TKIs even though TKIs failed as a first-line treatment. Currently, a number of phase III clinical trials using a combination of molecularly targeted therapies and immunotherapies are being conducted. If one or more of them also show positive results, the choice of preferred treatment will depend substantially on patient characteristics, tolerability and toxicity profile, and the preferred strategy would offer concrete experience to draw upon for HCC patients in the LT setting.

Growing evidence indicates that the gut microbiota affects the liver microenvironment in allograft rejection and HCC development[75-77]. Recently, several human studies have suggested that increased microbial diversity exerts a profound effect on the response to PD-1 inhibitors, which might be mediated by increased intratumor CD8+ T cell infiltration[78-80]. However, which specific bacterial taxa contribute to an improved tumor response to PD-1 inhibitors remains an unsolved issue. Hence, fecal microbiota transplantation (FMT), which shifts the entire gut microbiota to patients, may be an alternative. In the liver transplant setting, PD-1 inhibitors in combination with FMT might substantially improve the tumor response and allograft rejection, but more prospective studies are required.

Biomarkers for the response to immunotherapy

Effective biomarkers for identifying potential responders to ICIs would allow physicians to select optimal candidates for immunotherapy. PD-L1 expression on tumor cells was reported to be associated with the tumor response to PD-1 inhibitors [81]; however, in contrast, the CHECKMATE-040 trial suggested that the tumor response occurred regardless of PD-L1 staining[82]. Thus, PD-L1 expression in tumor

tissues does not seem sufficient as a single predictor to identify potential responders to PD-1 blockade. It is thought that immunotherapies, particularly ICIs, work in part by reactivating preexisting TILs. TILs are a class of lymphocytes in the tumor microenvironment that affect carcinogenesis and include CD8+ T cells, CD4+ T cells, tumor-associated macrophages (TAMs), tumor-associated neutrophils, myeloid-derived suppressor cells (MDSCs) and NK cells. An increased density of specific TIL phenotypes, particularly activated CD8+ TILs, is correlated with small tumor size, early TNM stage and better prognosis in HCC patients[83], and the CD8+ TIL density of responders was higher than that of nonresponders[84]. In addition, positive TILs in the tumor margin might be more associated with the tumor response than those in the tumor center[85,86]. In the tumor microenvironment, CD8+ TILs are exhausted or dysfunctional. The failure of CD8+ TILs to kill tumor cells involves signals from multiple cells, including MDSCs, Tregs, and TAMs. The interaction of PD-L1 with PD-1 on CD8+ TILs causes suppression and a decrease in their effector function, leading to decreased tumor cell death. Furthermore, the galectin-9 and T cell immunoglobulin and mucin-domain containing (TIM)-3 interaction on MDSCs and IL-10 secretion by Tregs have a similar effect[87]. Therefore, TILs and PD-L1 should be combined to guide the development of immunotherapies and predict their clinical responses in cancers. A recent study by DeLeon *et al*[60], covering 5 recipients with PD-L1 staining and 4 with TIL assessments, presumed that the combined expression of PD-L1 and TILs might be more reliable in liver transplant recipients. Additionally, the KEYNOTE-224 trial established a score involving both PD-L1-positive tumor cells and the immune cell ratio to the total number of viable tumor cells, with a positive score indicating a higher likelihood of tumor response[88]. In addition to the markers mentioned above, microsatellite instability, mismatch repair deficiency, and tumor mutational burden were thought to be potential biomarkers for predicting the response to ICIs; however, whether these biomarkers work well in the liver transplant setting requires further investigation. Some predictive biomarkers have been proposed to identify which patients are likely to benefit from CTLA-4 blockade; these include the absolute lymphocyte count and T cell activation marker-inducible costimulator [89]. However, to date, no biomarker has been validated in liver transplant recipients with CTLA-4 blockade. Herein, given the frustration with the inability to identify specific responder subsets, PD-1 inhibitors might be taken into consideration prior to CTLA-4 inhibitors to maximize tumor response. In addition, it is recommended that liver biopsy be conducted both pre- and postimmunotherapy together with a relevant biomarker quantitative assessment for a better stratification of HCC patients after LT.

CONCLUSION

Within the last decade, breakthroughs in immunotherapy have greatly expanded the treatment armamentarium for HCC. However, there is still an unlit corner for HCC patients awaiting LT or after LT due to the deep concern about lethal rejection induced by immunotherapy. On the one hand, there will be an increasing number of HCC patients after immunotherapy who are bridged or downstaged to be candidates for LT, as immunotherapy is now gradually becoming a part of routine or even preferred regimens for HCC systemic therapy. There are also many patients with HCC recurrence after LT who fail to respond to other therapies, and immunotherapy may be their last option. We must face the demand for immunotherapy in the setting of LT. On the other hand, the rejection rate, especially the lethal pattern, is higher than we can afford, and there are many unsolved problems when immunotherapy coexists with immunosuppressants in the setting of LT. Therefore, we need to explore immunotherapies in LT for HCC with caution regarding immunosuppressant adjustment, biomarkers for safety and efficacy, and selection strategies for different immunotherapies and patients.

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