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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

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SCIENTOMETRICS

Immunotherapy after liver transplantation: Where are we now?

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Abstract

BACKGROUND

There is limited evidence on the safety of immunotherapy use after liver transplantation and its efficacy in treating post-liver transplant hepatocellular carcinoma (HCC) recurrence.

AIM

To assess the safety of immunotherapy after liver transplant and its efficacy in treating post-liver transplant HCC recurrence.

METHODS

A literature review was performed to identify patients with prior liver transplantation and subsequent immunotherapy. We reviewed the rejection rate and risk factors of rejection. In patients treated for HCC, the oncological outcomes were evaluated including objective response rate, progression-free survival (PFS), and overall survival (OS).

RESULTS

We identified 25 patients from 16 publications and 3 patients from our institutional database (total n = 28). The rejection rate was 32% (n = 9). Early mortality occurred in 21% (n = 6) and was mostly related to acute rejection (18%, n = 5). Patients who developed acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, P = 0.02) and their graft biopsies might be more frequently programmed death ligand-1-positive (100% *vs* 33%, P = 0.053). Their PFS (1.0 ± 0.1 mo *vs* 3.5 ± 1.1 mo, P = 0.02) and OS (1.0 ± 0.1 mo *vs* 19.2 ± 5.5 mo, P = 0.001) compared inferiorly to patients without rejection. Among the 19 patients treated for HCC, the rejection rate was 32% (n = 6) and the overall objective response rate was 11%. The median PFS and OS were 2.5 ± 1.0 mo and 7.3 ± 2.7 mo after immunotherapy.

CONCLUSION

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Rejection risk is the major obstacle to immunotherapy use in liver transplant recipients. Further studies on the potential risk factors of rejection are warranted.

Key Words: Liver transplant; Hepatocellular carcinoma; Recurrence; Immunotherapy; Rejection; Survival

Core Tip: A literature review was performed to identify patients with prior liver transplantation and subsequent immunotherapy. Among the 28 included patients, the rejection rate was 32% (n = 9). Patients who developed acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, P = 0.02) and their graft biopsies might be more frequently programmed death ligand-1 positive (100% *vs* 33%, P = 0.053). Among the 19 patients treated for hepatocellular carcinoma (HCC), the overall objective response rate was 11%. Rejection risk is the major obstacle to immunotherapy for post-liver transplant HCC recurrence.

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INTRODUCTION

Post-liver transplant hepatocellular carcinoma (HCC) recurrence represents a therapeutic challenge. Prognosis is generally poor while tumor progression is unrestrained with suppressed host immunity. Thanks to recent advances in oncological treatment and improved immunosuppression, the outlook of these patients has improved[1,2], and long-term survival is no longer impossible. Nevertheless, reduced immune surveillance remains the Achilles heel for tumor control.

Over the last decade, immunotherapy has revolutionized cancer treatment. By disengaging immune checkpoints pathways, host immune response is augmented and directed towards the tumor. Immunotherapy is also characterized by a favorable side-effect profile compared to targeted therapy, which has been extensively investigated for post-transplant HCC recurrence. Modest efficacy was observed, but significant adverse effect has often led to dose reduction or discontinuation[3-6]. While immunotherapy has demonstrated satisfactory outcomes in patients with advanced primary HCC[7,8], its role in post-transplant HCC recurrence has not been investigated. There are two major obstacles to immunotherapy use in this setting. First, the possibility of enhancing alloimmunity and inducing rejection has raised safety concern. Second, efficacy is also questionable because concomitant immunosuppression potentially interferes with the immunomodulatory pathways involved. Given these concerns, liver transplant patients have been excluded from cancer immunotherapy trials, and limited data exist on the role of immune checkpoint inhibitors for post-liver transplant HCC recurrence.

In this study, we reviewed the literature for the record of patients who had undergone prior liver transplantation and received immunotherapy. In addition, we reviewed the liver transplant recipients who had been treated with immunotherapy in our institution. The objective was to summarize the existing experience and provide further insights on safety and efficacy of immunotherapy for post-transplant HCC recurrence.

MATERIALS AND METHODS

Patients

A literature search was performed on PubMed (United States National Library of

Medicine, National Institutes of Health, United States) for relevant English articles with a combination of keywords: "liver transplantation" with "immunotherapy" or "checkpoint inhibitors" or "programmed cell death 1" or "PD-1" or "cytotoxic T lymphocyte associated 4" or "CTLA-4." The full text of potentially relevant articles was reviewed. Original case reports, case series, observation studies, and review articles were included if they described immune checkpoint inhibitor therapy in a patient with prior liver transplantation. Laboratory studies without clinical subjects were excluded. References in the included studies were reviewed for additional relevant articles. Patient data was extracted including demographics, timing and indication of immunotherapy, concomitant immunosuppression, programmed death ligand-1 (PD-L1) status, adverse events, treatment response, and survival. Subjects were cross-checked to ensure no individual patient was included twice. In addition, we reviewed the records of liver transplant recipients who underwent immunotherapy in Queen Mary Hospital, the University of Hong Kong during the period from January 2016 to December 2020. Patient data were retrieved from a prospectively maintained institutional database.

Methods and statistics

We assessed the safety of immunotherapy by reviewing the rejection rate and mortality in all identified patients treated for various indications. We also looked into patients treated for recurrent HCC after liver transplantation to investigate the efficacy of immunotherapy in this setting. We reviewed the best treatment response, rate of early mortality, progression-free survival (PFS), and overall survival (OS) after immunotherapy. Early mortality was defined as mortality within 30 d from immunotherapy. Treatment response was defined according to the Response Evaluation Criteria in Solid Tumors 1.1[9]. Data was summarized with descriptive statistics. Continuous variables were expressed with medians and interquartile ranges (IQRs). Parametric and non-parametric variables were compared with the Student's *t*-test and Mann-Whitney *U* test where appropriate. Categorical variables were expressed in frequencies and percentages and were compared with the chi-square test. Survival data was analyzed with the Kaplan-Meier method and compared using the log-rank test. Data were analyzed using Statistical Package for the Social Sciences 16.0 (SPSS) for Windows (SPSS Inc., Chicago, IL, United States). Statistical significance was defined by $P < 0.05$.

RESULTS

Using PubMed, we identified 16 publications describing 25 patients who had a prior liver transplantation and subsequently received immunotherapy[10-25]. From the institutional database, there were 3 patients fulfilling the same inclusion criteria. These 28 patients formed the basis of this study (Table 1).

Patient characteristics

The descriptive characteristics are shown in Table 2. There was a male predominance (79%), and the median age was 61 (IQR 53-66). Nineteen patients (68%) were treated for recurrent HCC, 8 (29%) for *de novo* melanoma, and 1 (4%) for squamous cell carcinoma of the lung. Most received immunotherapy after failure of prior systemic therapy (median line of systemic treatment 2, IQR 1-3). Twenty-five patients (89%) received a programmed cell death protein-1 (PD-1) inhibitor (nivolumab 54%; pembrolizumab 36%). Four patients (14%) received cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor (ipilimumab) and they were all indicated for melanoma. One patient received ipilimumab followed by pembrolizumab.

Seven graft liver and eight tumor tissues were tested for PD-L1 status. Among the tested samples, the rates of positive PD-L1 staining were 71% for graft liver and 50% for tumor. Ten patients (36%) received tacrolimus monotherapy as immunosuppression. Six patients (21%) received a mammalian target of rapamycin (mTOR) inhibitor as single agent while 5 patients (18%) received combination therapy with tacrolimus and an mTOR inhibitor.

Graft rejection and associated factors

The rate of acute rejection following immunotherapy was 32% ($n = 9$). Early mortality occurred in 21% ($n = 6$), and most were related to acute rejection (18%, $n = 5$). Patients who developed acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, $P = 0.02$). Among the patients with

Table 1 Patients with prior liver transplantation and subsequent immunotherapy

Ref.	Drug	No. of cycles	Sex	Age	Indication	Year from transplant	Line of therapy	Rejection	Early mortality	PD-L1 status		Immunosuppression	Best response	PFS (mo)	OS (mo)
										Graft	Tumor				
De Toni and Gerbes[10]	Nivolumab	15	M	41	HCC	NA	1	No	No	NA	0%	Tacrolimus	PD	3.5	7
Friend *et al*[11]	Nivolumab	2	M	20	HCC	4	2	Yes	Yes	Pos	Pos	Sirolimus	NA	1	1
Friend *et al*[11]	Nivolumab	1	M	14	HCC	3	3	Yes	Yes	Pos	Pos	Tacrolimus	NA	1	1
Varkaris *et al*[12]	Pembrolizumab	NA	M	70	HCC	8	NA	No	No	NA	NA	Tacrolimus	PD	NA	NA
Munker and De Toni[13]	Nivolumab	NA	M	57	HCC	2.7	3	No	No	NA	10%	Tacrolimus	PD	2.2	1.2 (surviving)
Munker and De Toni[13]	Nivolumab	NA	M	56	HCC	7.8	4	No	No	5%	NA	Sirolimus/MMF	PD	0.7	1.1 (surviving)
Munker and De Toni[13]	Nivolumab	NA	F	35	HCC	3.7	5	No	No	0%	0%	Tacrolimus	PD	1.3	1.3 (surviving)
Munker and De Toni[13]	Nivolumab	NA	M	64	HCC	1.2	2	No	Yes	NA	0%	Tacrolimus	NA	0.3	0.3
Munker and De Toni[13]	Nivolumab	NA	M	68	HCC	1.1	2	Yes	Yes	30%	0%	Sirolimus	NA	0.9	0.9
Al Jarroudi *et al*[14]	Nivolumab	4	M	70	HCC	2.75	3	Yes	No	NA	NA	Tacrolimus	NA	4	4
Al Jarroudi *et al*[14]	Nivolumab	5	F	62	HCC	1	4	No	No	NA	NA	Tacrolimus	PD	2.5	NA
Al Jarroudi *et al*[14]	Nivolumab	6	M	66	HCC	5	4	No	No	NA	NA	Tacrolimus	SD	3	NA
Rammohan *et al*[15]	Pembrolizumab	14	M	57	HCC	4.3	2	No	No	NA	NA	Tacrolimus/mTOR inhibitor	CR	10 (no progression)	10 (surviving)
Gassmann *et al*[16]	Nivolumab	1	F	53	HCC	3	2	Yes	Yes	NA	NA	Everolimus	NA	0.8	0.8
Nasr *et al*[17]	Pembrolizumab	35	M	63	HCC	4.6	2	No	No	NA	NA	Tacrolimus/MMF	CR	25 (no progression)	25 (surviving)
Wang *et al*[18]	Pembrolizumab	1	M	48	HCC	1	1	Yes	No	NA	NA	Tacrolimus/Everolimus	NA	NA	8 (surviving)
Au (current research)	Nivolumab	4	M	62	HCC	2.2	3	No	No	NA	NA	Tacrolimus/Everolimus	PD	4.0	7.3

Au (current research)	Nivolumab	6	M	53	HCC	6.0	2	No	No	NA	NA	Sirolimus	PD	2.8	10.6
Au (current research)	Pembrolizumab	16	M	77	HCC	32	1	No	No	NA	NA	Tacrolimus/Everolimus	SD	12.4	19.2
Ranganath and Panella[19]	Ipilimumab	4	F	59	Melanoma	8	NA	No	No	NA	NA	Sirolimus	PR	5	9 (surviving)
Morales *et al*[20]	Ipilimumab	4	M	67	Melanoma	8	2	No	No	NA	NA	Sirolimus/MMF	PR	4 (no progression)	14 (surviving)
Munker and De Toni[13]	Pembrolizumab	NA	M	55	Melanoma	5.5	2	No	No	0%	5%	Everolimus/MMF	CR	21.1 (no progression)	21.1 (surviving)
Munker and De Toni[13]	Pembrolizumab	NA	M	64	Melanoma	3.1	2	Yes	No	25%	NA	MMF/Prednisolone	NA	NA	0.7 (surviving)
Kuo *et al*[21]	Ipilimumab/Pembrolizumab	4/25	M	62	Melanoma	6	NA	No	No	NA	NA	Sirolimus	PR	24 (no progression)	24 (surviving)
Dueland *et al*[22]	Ipilimumab	1	F	67	Melanoma	1.5	1	Yes	No	NA	NA	Prednisolone	PD	3 (no progression)	4
Schvartsman *et al*[23]	Pembrolizumab	2	M	35	Melanoma	20	1	No	No	NA	NA	Tacrolimus	CR	6	6 (surviving)
Tio *et al*[24]	Pembrolizumab	1	F	63	Melanoma	NA	NA	Yes	Yes	NA	NA	Ciclosporin	NA	NA	NA
Biondani *et al*[25]	Nivolumab	3	M	54	SCC lung	13	1	No	No	NA	NA	Tacrolimus/Everolimus	PD	2.25	15

CR: Complete response; F: Female; HCC: Hepatocellular carcinoma; M: Male; NA: Not available; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SCC: Squamous-cell carcinoma; SD: Stable disease.

acute rejection, graft PD-L1 positivity was possibly more frequent but not statistically evident (100% *vs* 33%, $P = 0.053$). Otherwise, patients with and without rejection were comparable in terms of age (63 *vs* 59, $P = 1.00$), indication of immunotherapy ($P = 0.93$), proportion of PD-1 *vs* CTLA-4 blockade ($P = 1.00$), and immunosuppressive therapy received ($P = 0.29$-0.48). Excluding one patient who received both PD-1 and CTLA-4 blockade, the rejection rate was similar between patients receiving PD-1 (8/24) and CTLA-4 blockade (1/3) (both 33%, $P = 1.00$).

Patients with acute rejection suffered from more early mortalities (56% *vs* 5%, $P = 0.002$). Their PFS (1.0 ± 0.1 mo *vs* 3.5 ± 1.1 mo, $P = 0.02$) and OS (1.0 ± 0.1 *vs* 19.2 ± 5.5 mo, $P = 0.001$) compared inferiorly to patients without rejection (Figures 1 and 2).

Efficacy in treating recurrent HCC

Patients who received immunotherapy for HCC recurrence were treated with immunotherapy earlier after transplant than those treated for *de novo* malignancies (median time from transplant 3.3 years *vs* 7 years, $P = 0.03$). They received immuno-

Table 2 Descriptive characteristics of all patients with prior liver transplantation and subsequent immunotherapy

	All	Rejection	No rejection	*P* value
Total (%)	28	9 (32)	19(68)	
Gender (M/F; %M)	22/6 (79)	6/3 (67)	16/3 (84)	0.29
Age	61 (53-66)	63 (34-67.5)	59 (54-64)	1.00
Year after transplant	3.9 (2.5-6.5)	2.9 (1.2-3.1)	5.3 (2.7-8.0)	0.02
Indication (%)				0.93
HCC	19 (68)	6 (67)	13 (68)	
Melanoma	8 (29)	3 (33)	5 (26)	
SCC of lung	1 (4)	0 (0)	1 (5)	
Line of systemic therapy	2 (1-3)	2 (1-3)	2 (1-4)	0.52
Immunotherapy by drug (%)				0.92
Nivolumab	15 (54)	5 (56)	10 (53)	
Pembrolizumab	10 (36)	3 (33)	7 (37)	
Ipilimumab	4 (14)	1 (11)	3 (16)	
Immunotherapy by class (%)				1.00
PD1/PD-L1	24 (86)	8 (89)	16 (84)	
CTLA-4	3 (11)	1 (11)	2 (11)	
Both	1 (4)	0 (0)	1 (5)	
PD-L1 positivity (%)				
Graft	5/7 (71)	4/4 (100)	1/3 (33)	0.053
Tumor	4/8 (50)	2/3 (67)	2/5 (40)	0.47
Immunosuppression (%)				
Single agent tacrolimus	10 (36)	2 (22)	8 (42)	0.31
Single agent mTOR-inhibitor	6 (21)	3 (33)	3 (16)	0.29
Tacrolimus with mTOR-inhibitor	5 (18)	1 (11)	4 (21)	0.52
Others	7 (25)	3 (33)	4 (21)	0.48
Acute rejection (%)	9 (32)			
Mortality in 30 d (%)	6 (21)	5 (56)	1 (5)	0.002
Progression-free survival	3 ± 0.6	1.0 ± 0.1	3.5 ± 1.1	0.02
Overall survival	10.6 ± 5.3	1.0 ± 0.1	19.2 ± 5.5	0.001

CTLA-4: Cytotoxic T-Lymphocyte antigen-4; F: Female; HCC: Hepatocellular carcinoma; M: Male; mTOR: Mammalian target of rapamycin; PD-1: Programmed cell death protein-1; PD-L1: Programmed death ligand-1; SCC: Squamous-cell carcinoma.

therapy as a median of second-line systemic therapy (IQR 1-3) (Table 3). Six patients (32%) suffered rejection and one patient (5%) suffered early mortality unrelated to rejection. Treatment response was not evaluated for these patients. The proportion of patients with complete response, partial response, stable disease, and progressive disease were 11% (n = 2), 0% (n = 0), 11% (n = 2), and 42% (n = 8) respectively. The overall objective response rate was 11%. The median PFS and OS were 2.5 ± 1.0 and 7.3 ± 2.7 mo after immunotherapy.

We compared the relative efficacy of nivolumab and pembrolizumab for recurrent HCC after liver transplantation. Pembrolizumab was used as an earlier line of therapy (median third line *vs* second line, P = 0.03). Pembrolizumab was associated with a higher complete response (0% *vs* 40%, P = 0.03), less progressive disease (50% *vs* 20%, P = 0.03), and better PFS (1.3 ± 1.1 *vs* 12.4 mo, P = 0.004) and OS (4.0 ± 3.4 *vs* 19.2 mo, P = 0.006). Pembrolizumab was potentially associated with fewer early mortalities but this was not statistically evident (36% *vs* 0%, P = 0.12).

Table 3 Descriptive characteristics of patients with immunotherapy for post-transplant hepatocellular carcinoma recurrence

	All	Nivolumab	Pembrolizumab	*P* value
Total (%)	19	14 (74)	5 (26)	
Rejection (%)	6 (32)	5 (36)	1 (20)	0.52
Early mortality (%)	5 (26)	5 (36)	0 (0)	0.12
Line of systemic therapy	2 (1-3)	3 (2-4)	2 (1-2)	0.03
Tumour PD-L1 positivity (%)	3/7 (43)	3/7 (43)	0/0 (-)	
Best treatment response (%)				
Complete response	2 (11)	0 (0)	2 (40)	0.03
Partial response	0 (0)	0 (0)	0 (0)	0.64
Stable disease	2 (11)	1 (7)	1 (20)	0.58
Progressive disease	8 (42)	7 (50)	1 (20)	0.03
Progression-free survival	2.5 ± 1.0	1.3 ± 1.1	12.4	0.004
Overall survival	7.3 ± 2.7	4.0 ± 3.4	19.2	0.006

PD-L1: Programmed death ligand-1.

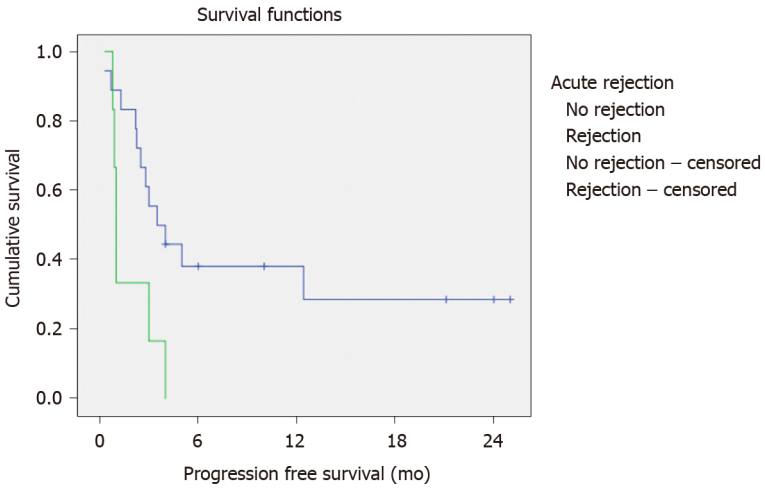

Figure 1 Progression-free survival of all patients stratified by the presence of rejection (*P* = 0.02).

DISCUSSION

We found that immunotherapy could be associated with fatal graft rejection. The rejection rate was relatively high (32%), and more importantly, was associated with a high rate of organ failure and early mortality (56% in patients with rejection). A more malignant clinical course was observed opposed to spontaneous acute rejection, which was usually treatment responsive and seldom resulted in irreversible consequences [26-28]. To optimize patient selection, we investigated the potential clinical factors associated with acute rejection in the identified patient sample. These factors included the timing of immunotherapy, the role of PD-1 *vs* CTLA-4 blockade, the effect of PD-L1 positivity on the liver graft biopsy, and the strength of the immunosuppressive regimen during immunotherapy.

We observed that patients with long-term liver transplantation were less liable to rejection when treated with immunotherapy. From our cohort, patients with rejection received immunotherapy earlier after transplantation (median time from transplant 2.9 years *vs* 5.3 years, $P = 0.02$). After transplant, immune tolerance towards the liver graft increases with time[29,30]. The underlying mechanism is the dissemination and persistence of donor leukocytes from the liver graft to the recipient, leading to systemic chimerism[31]. This explains why most spontaneous acute rejection occurs

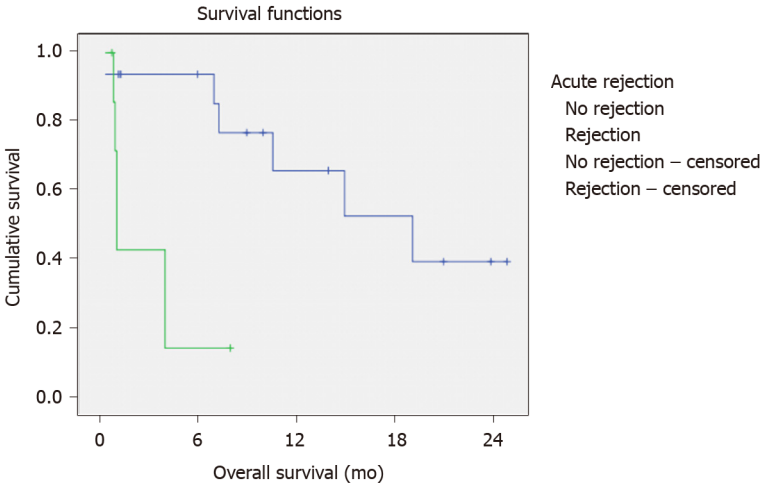

Figure 2 Overall survival of all patients stratified by the presence of rejection (*P* = 0.001).

early after liver transplant[32], allowing immunosuppression to be tapered with time. The protective effect of time was consistently observed in the setting of immunotherapy, however to a lesser extent. While the risk of spontaneous rejection is largely reduced beyond the first year after transplant[32], the risk of post-immunotherapy rejection persists further. Patients who developed post-immunotherapy rejection were given immunotherapy at a median time of 2.9 years after transplant. Existing data are too limited to conclude the safe time interval before immunotherapy that can safely be used. However, it appears that the risk of rejection cannot be neglected in the first few years after transplantation.

Most HCC recurrence occurs early after liver transplantation[33]. From the current series, patients who received immunotherapy for HCC recurrence were treated with immunotherapy earlier after transplant than those treated for *de novo* malignancies (median time from transplant 3.3 years *vs* 7 years, $P = 0.03$). From our experience, patients with early HCC recurrence also have a poorer prognosis[1]. While the use of immunotherapy for post-transplant HCC recurrence is investigational, it is reasonable to reserve immunotherapy to patients with late recurrence. With reduced rejection risk and better tumor biology, better outcomes can be expected.

Researchers have proposed that PD-1 inhibition is potentially associated with a higher risk of rejection and graft loss compared to CTLA-4 blockade[34]. In a cohort of 12 transplant recipients, rejection occurred in 4 of the 8 patients receiving anti-PD-1 therapy but in none of the 4 patients receiving anti-CTLA-4 treatment[35]. It is hypothesized that the PD-1 pathway plays a more integral role in allograft immune tolerance[35,36]; however, our data did not support this hypothesis. In the current cohort, patients who received anti-PD-1 agents had a rejection rate that was very similar to those receiving CTLA-4 blockade (33% *vs* 33%, $P = 1.00$). In comparison, our study was characterized by inclusion of liver transplant recipients only, and a better sample size ($n = 28$). Though insufficient to indicate the relative safety profile of both classes of immune checkpoint inhibitor, our observation showed that CTLA-4 blockade is not without risk of liver graft rejection. Given its established efficacy in primary HCC, anti-PD-1 agents should remain the agent of choice when immunotherapy is contemplated for treatment of post-transplant HCC recurrence[7,8].

Allograft PD-L1 staining was evaluated in 7 patients treated with immunotherapy. Patients with rejection were more frequently observed to have positive graft PD-L1 staining, though statistical significance was not reached. Our data are suggestive of a potential role of graft PD-L1 positivity predicting rejection. However, many of these allograft biopsies were taken during rejection. To allow risk stratification before commencement of therapy, a baseline allograft biopsy may be more valuable. In our institution, protocolled graft biopsy is taken during transplant after implantation. To better study the significance of graft PD-L1 status, these implant biopsies could be reviewed for PD-L1 status when immunotherapy is contemplated.

Immunosuppression is usually tapered upon diagnosis of cancer to preserve anti-tumor immunity[33]. Upon recurrence, some patients had calcineurin inhibitors weaned off and were maintained on an mTOR-inhibitor. In these patients, we did not observe a higher rejection rate following immunotherapy. However, the current study was underpowered to compare heterogenous immunosuppressive regimens. Dosage

and drug level information was also incomplete for evaluation. The ideal immunosuppression for patients undergoing immunotherapy requires extensive investigation into the interaction between anti-tumor immunity and alloimmunity, which warrants future laboratory and clinical studies.

In non-organ transplant recipients, mild immune-related adverse events can often be observed or treated with steroids while continuing immunotherapy[37]. Although antagonizing mechanisms between immune checkpoint inhibitor and steroid have been described in cellular models[38], clinical studies have not consistently concluded a nefarious interaction between them[39]. In contrast, liver transplant recipients often suffer irreversible liver failure after immunotherapy induces graft rejection, despite high doses of steroid and prompt withdrawal of immunotherapy. Given the serious consequences of graft rejection, continuation of immunotherapy could not be recommended based on the current experience.

The overall response rate for immunotherapy for post-transplant HCC recurrence was low (11%). A significant proportion of patients developed rejection (32%), leading to mortality or premature discontinuation of treatment. These results suggest that safety of immunotherapy must be addressed before its potential efficacy can be fully assessed. Of note, the 5 patients who received pembrolizumab had a better overall response rate and survival. The comparably lower rate of rejection (36% *vs* 20%, P = 0.52) could have partly contributed. However, pembrolizumab was commenced earlier in the course of disease, while nivolumab was usually given after failure of multiple lines of systemic therapy. The disease status of these patients was not available for comparison. Their potential confounding effects should be considered when interpreting the outcomes. In the current series, patient numbers were too limited to assess the relationship between tumor PD-L1 status and treatment response. In future studies, explant tumor PD-L1 status can be reviewed when patients are contemplated for immunotherapy.

The current study was limited by its methodology. Subjects were sampled from individual case reports and series with low homogeneity, and data analysis is vulnerable to publication bias. Patients with extreme outcomes were preferentially reported and the rejection rate could have been overestimated. The included patients had heterogenous immunosuppressive regimen, which potentially affect rejection and tumor response. The small sample size largely limited the analytical power.

CONCLUSION

From the limited experience in the literature, we conclude that rejection remains the major obstacle to immunotherapy use in the setting of post-liver transplant HCC recurrence. It is associated with considerable risk of organ failure and mortality. Before immunotherapy can be recommended for post-transplant HCC recurrence, it is essential to determine which patients are at risk of developing rejection. We have identified a short duration from transplant and graft PD-L1 positivity as potential risk factors. We suggest establishing an international registry to allow information regarding immunotherapy for post-liver transplant HCC recurrence to be systemically collected. With better understanding and insights, we could better select the suitable patients and achieve more desirable outcomes.

ARTICLE HIGHLIGHTS

Research background

Evidence on the safety of immunotherapy in liver transplant recipient is limited. Its efficacy on treating post-liver transplant hepatocellular carcinoma (HCC) recurrence is unknown.

Research motivation

To study the potential role of immunotherapy in the setting of post-liver transplant HCC recurrence.

Research objectives

To assess the safety of immunotherapy after liver transplantation and to assess its efficacy on treating post-liver transplant HCC recurrence.

Research methods

A review of current literature describing immune checkpoint inhibitor therapy in a patient with prior liver transplantation. Patients from our institution were included for review.

Research results

There were 28 patients identified. The rejection rate was 32% (n = 9). Early mortality occurred in 21% (n = 6) and were mostly related to acute rejection (18%, n = 5). Patients with acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, P = 0.02). Their progression-free survival (1.0 ± 0.1 *vs* 3.5 ± 1.1 mo, P = 0.02) and overall survival (1.0 ± 0.1 *vs* 19.2 ± 5.5 mo, P = 0.001) compared inferiorly to patients without rejection. Among the 19 patients treated for HCC, the rejection rate was 32% (n = 6) and the overall objective response rate was 11%.

Research conclusions

Rejection risk is the major obstacle to immunotherapy use in liver transplant recipients.

Research perspectives

Further studies on the potential risk factors of rejection are warranted.

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