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Current Status of the Application of Immune Checkpoint Inhibitors in Liver Transplantation for Hepatocellular Carcinoma

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1. Abstract

Immune Checkpoint Inhibitors (ICIs) are one of the effective treatments for patients with advanced hepatocellular carcinoma and effectively prolong their survival. However, it is still controversial whether ICIs can be used in liver transplantation for hepatocellular carcinoma. Long-term use of immunosuppressive drugs is required in liver transplant patients with hepatocellular carcinoma, and the use of ICIs will enhance immune function and may increase the occurrence of immune rejection. This article summarizes the clinical evidence of the application of ICIs before and after liver transplantation for hepatocellular carcinoma, and discusses the safety and efficacy influencing factors of the application of ICIs before and after liver transplantation for hepatocellular carcinoma, providing the basis for clinical practice and clinical research.

2. Introduction

Hepatocellular Carcinoma (HCC), causing almost 0.7 million deaths annually, has bring a heavy burden to the human society. Comprehensive treatment programs such as liver resection, liver transplantation, ablation, hepatic artery embolization, targeted therapy and immunotherapy are often adopted in clinical practice. With the advantages of complete removal of tumors, curing of liver cirrhosis, and elimination of hepatitis B virus, liver transplantation has become one of the most effective treatment options. The 1-year and 5-year survival rates are 85-90% and 70-75%, respectively, and the 5-year recurrence rate is only 16% [1, 2]. Immune checkpoint inhibitors (ICIs), a new type of anti-tumor drug, have been widely used in the combined treatment of advanced hepatocellular carcinoma in the down-stage treatment and pre- and post-operative adjuvant treatments in recent years. After liver transplantation, patients need to maintain immunosuppression, but ICIs may induce rejection by activating the immune response, leading to inactivation of the graft. Therefore, the application of ICIs before and after liver transplantation is still full of controversy. This article will review the application of ICIs before and after liver transplantation for hepatocellular carcinoma.

3. Mechanisms of ICIs

Immune Checkpoints (ICs) are pathway proteins that inhibit immune regulation during the immune response. Mostly located on the surface of activated lymphocytes and tumor cells, they can protect tumor cells from the attack of immune cells, helping tumor cells escape immune surveillance. ICIs, a class of monoclonal antibodies that target immune checkpoints that inhibit T cell activation, is able to promote T cell-mediated tumor cell clearance by blocking inhibitory signaling pathways [3]. ICIs are mainly divid-

ed into two types: one is the monoclonal antibody that acts on the programmed death protein-1 (PD-1) pathway, such as nivolumab, keytruda, sintilimab, pembrolizumab and camrelizumab, or antibody of programmed cell death protein ligand 1 (PD-L1) such as atezolizumab and avelumab, etc. The other type acts on cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), such as ipilimumab and tremelimumab [2].

PD-1 can inhibit the downstream phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) signaling pathway through binding to PD-L1, and then inhibits the expression of Bcl-xl, thereby promoting the apoptosis of T lymphocytes and inhibiting the secretion of cytokines by T lymphocytes [4]. In addition, the PD-1/PD-L1 pathway can also induce the differentiation of effector T cells into regulatory T cells (Tregs) [5]. Tregs play an important role in transplantation immune tolerance. CD8+CD5RClowTreg and plasmacytoid dendritic cells (pDC) together form the regulatory network of immune tolerance which plays a negative immune regulatory role [6]. Researchers have found that patients with immune tolerance after liver transplantation have higher Tregs levels, while patients with rejection reactions have significantly lower Tregs levels. Patients with additional Treg infusions can completely or partially stop immunosuppressive drugs [7]. Therefore, PD-1/PD-L1 antibody can relieve the immune checkpoint on T cell activation, proliferation, and cytokine release, which can enhance the anti-tumor immune response and restore T cell immune function, so as to inhibit the occurrence and development of tumors[8].

CTLA-4, a type I transmembrane protein of the immunoglobulin superfamily usually present in the cytoplasm of CD4+ and CD8+ T cells It can be induced to the surface of T cells and compete with CD28 for binding to antigen-presenting cell surface ligands CD80 and CD86, thereby inhibiting the activity of toxic T cells and enhancing the immunosuppressive activity of Treg cells, resulting in the suppression of immune response of T cells. CTLA-4 has stronger binding ability with CD80 and CD86, and is able to directly remove the ligand from the surface of antigen presenting cells, preventing the ligand from binding to CD28, leading to the down-regulation of immune function of T cells [9].

4. Application of ICIs in the Advanced Hepatocellular Carcinoma Treatment

Anthony et al. conducted a phase 1/2 clinical trial using nivolumab in adults (≥18 years of age) with advanced hepatocellular carcinoma. Nivolumab treatment can significantly shrink the tumors of patients with advanced hepatocellular carcinoma, with an objective response rate of 15- 20%, which has a positive impact on overall survival [10]. In the global multicenter, open-label, randomized controlled phase III trial of IMbrave150, the clinical outcomes of atezolizumab combined with bevacizumab (T + A) and sorafenib in patients with unresectable hepatocellular carcinoma were evaluated, the objective response rate of patients in the "T + A" regimen was 30%, about 3 times that of patients in the traditional targeted therapy sorafenib group (11%), and the 56% of patients in the response group was still sustained, higher than 28% in the sorafenib group, reflecting the advantage that the "T + A" regimen can bring long-term benefits to patients. The data showed that the overall survival of patients treated with "T + A" regimen was 19.2 months, and the overall survival of patients in China reached 24.0 months [11]. The "2021 European Society of Medical Oncology Hepatocellular Carcinoma Clinical Practice Guidelines Update" recommends atilizumab combined with bevacizumab as the first-line treatment [12]. The domestic expert consensus "Chinese Expert Consensus on Transformation Therapy of Advanced Hepatocellular Carcinoma Based on Immune Combination Targeting Program (2021 Edition)" pointed out that ICIs combined with anti-angiogenesis targeted drug therapy as a conversion program for advanced hepatocellular carcinoma is worth trying. The specific plan for example, pembrolizumab combined with lenvatinib, atilizumab combined with bevacizumab, carrelizumab combined with apatinib and other combination programs, etc. The higher the objective response rate of the combined treatment plan, the more potential it is to successfully transform advanced hepatocellalar carcinoma, and the more it is worth trying.

5. Preoperative Application of ICIs in Liver Transplantation Patients with Hepatocellular Carcinoma

There are not many studies on the use of ICIs before liver transplantation. Parissa et al. summarized the application of nivolumab as preoperative treatment for transplant patients at the Recanati/Miller Transplant Institute in the United States between 2017 and 2020. The immunosuppressive drug was a steroid (500 mg methylprednisolone), and the dose was gradually reduced to Prednisone (10 mg/day), while taking mycophenolate mofetil (1 g/twice/day) and maintaining tacrolimus concentration (10-12 ng/mL). During the 16-month follow-up after transplantation, there was no serious rejection, tumor recurrence or death [13]. Nordness et al. reported one patient was treated with nivolumab (240 mg/2 weeks) before liver transplantation, and the last administration was 8 days before the operation. The postoperative immunosuppressive regimen was tacrolimus, mycophenolate mofetil and prednisone. However, liver function continued to deteriorate after liver transplantation, and the patient died on the tenth day after the operation. [14] Chen et al. reported that a patient received 10 times of teriprilumab (4 weeks/course, 240 mg) 93 days before liver transplantation and intraoperative intravenous methylprednisolone 500 mg during surgery. After surgery, conventional maintenance immunosuppressive therapy (tacrolimus, methylprednisolone) was used, and the patient's liver function further deteriorated 33 hours after surgery and was treated with continuous renal replacement therapy (CRRT) + plasma exchange (2000 mL). At 40h after operation, the patient received plasma exchange (3000ml) and plasma-specific bilirubin adsorption. After CRRT again, the liver function continued to deteriorate. The patient died 71h after operation [15]. Qiao et al. conducted a

retrospective study to analyze 7 patients who were treated with pembrolizumab or carreizumab combined with lenvatinib before liver transplantation. The average interval between ICIs and liver transplantation was 1.3 months. The immunosuppressive regimen was sulfamethoxazole + tapering dose of corticosteroids. Long-term maintenance was combined or alone with corticosteroids, cyclosporine or tacrolimus, cilomox and motilocin. The objective response rate and disease control rate criteria were 71% and 85%, respectively, and biopsy confirmed rejection in only one patient (rejection rate was 14.3%), and administration of 500 mg methylprednisolone was started, then tapered and discontinued 16 days after surgery, and the serum total bilirubin level decreased to less than 100 μmol/L without subsequent increase [16]. Schwachaeipper et al. reported a 62-year-old male patient who was treated with nivolumab before liver transplantation for liver cancer, the patient partial responded and without rejection. The time interval between liver transplantation and ICIs use was 1.5years [17].

Dehghan et al. reported A 60-year-old female patient, was treated with nivolumab before liver transplantation. The immunosuppressive drugs were tacrolimus, MMF and steroid. Due to graft loss caused by rejection after liver transplantation, liver transplantation was performed again on the 34th day after operation. IV Immunoglobulin (IVIG), methylprednisolone and Anti-Thymocyte Globulin (ATG) were used for treatment. She was discharged on 33th day after re-transplantation, and still OK at 18th months [18].

In conclusion, the probability of rejection was 20% (4/20) in patients treated with ICIs before liver transplantation. It shows that patients treated with ICIs before surgery have a certain effect, but the consequences of graft rejection still cannot be ignored and close attention should be continued. In addition, for patients with graft rejection, preoperative treatment with ICIs followed by re-transplantation may be a treatment (Table 1).

Table 1: Characteristics of the patients receiving ICI before liver transplantation.

Year	Author	Age	Sex	ICI	Immunosuppresion drugs	Duration	response	Time between LT and ICI	rejection	last status
2021	Dehghan	60	F	Nivolumab	tacrolimus+MMF+steroid+ Methylprednisolone +IVIG	15month	N/A	N/A	NO	alive
2021	Parissa	69	M			23Day	N/A	18Day	NO	alive
		56	F			22Day	N/A	22Day	NO	alive
		58	M			22Day	N/A	1Day	NO	alive
		63	M			21Day	N/A	2Day	NO	alive
		30	M	Nivolumab	tacrolimus+MMF+steroid	16Day	N/A	22Day	NO	alive
		63	M			14Day	N/A	13Day	NO	alive
		66	M			14Day	N/A	253Day	NO	alive
		55	F			8Day	N/A	7Day	NO	alive
		53	F			8Day	N/A	30Day	NO	alive
2021	Chen	39	M	toripalimab	tacrolimus+steroid	10cycle	N/A	3month	Yes	Death
2021	Qiao	N/A	M	pembrolizumab/			PR%=	Mean:		
		N/A	M	camrelizumab			71%	1.3 month		
		N/A	M							
		N/A	M		N/A	1-5 cycle			1 patient	alive
		N/A	M							
		N/A	M							
		N/A	M							
2020	Schwachaeipper	62	M	Nivolumab	N/A	34cycle	PR	1.5Y	NO	alive
2019	Nordness	65	M	Nivolumab	tacrolimus+MMF+steroid	44cycle	PR	1.8Y	Yes	Death

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; N/A, not available
M, male; F, female; Y, year; MMF, Mycophenolate Mofetil

6. Postoperative Application of ICIs in Liver Transplantation Patients with Hepatocellular Carcinoma

Due to long-term immunosuppression, organ transplant recipients may develop extensive malignant tumors (including melanoma and blood cancer, etc.). In the patients who undergo transplantation due to hepatocellular carcinoma, the risk of recurrence after transplantation is increased to about 10% within 5 years [19]. Because of its potential clinical benefits, ICIs have been used as a salvage treatment option for many transplant patients since it was approved. In some cases, good tolerance and signs of anti-cancer efficacy are observed, but organ rejection often occurs. Amjad et al. reported that a female hepatocellular carcinoma patient experienced tumor metastasis one year after liver transplantation. After active treatment with nivolumab, the condition was effectively controlled and no rejection occurred [20]. Jarroudi et al reported that 3 patients with recurrent hepatocellular carcinoma after liver transplantation were treated with nivolumab (240 mg/2 weeks). None of these 3 patients had a rejection reaction, while no significant clinical benefit was observed unfortunately. [21] Gassmann et al. reported a case of recurrence of hepatocellular carcinoma after liver transplantation, and severe liver failure occurred 3 weeks after the use of nivolumab. They also summarized the rejection of 11 patients treated with ICIs after liver transplantation, of which 5 were treated with nivolumab, 3 were treated with ipilizumab, and 2 were treated with pembrolizumab. And 1 case was treated with ipilimumab combined with pembrolizumab. The prognostic results of the disease were 3 patients who were treated with ipilimumab, and the disease progressed. In patients with nivolumab, 3 cases are known to have progressed. As for patients who used ipilizumab and pembrolizumab in combination, after the first application of ipilizumab, there was no rejection reaction but the disease progressed, and then there was a partial response after the application of pembrolizumab. One patient receiving pembrolizumab had a complete radiological remission, and one patient had no melanoma for more than 6 months after stopping pembrolizumab [22]. Deleon et al.conducted a retrospective study, which included 7 patients with metastatic cancer who had a history of liver transplantation and were treated with PD-1 inhibitors, and 5 patients with hepatocellular carcinoma were treated with nivolumab. Two patients with melanoma were treated with pembrolizumab. Only 1 patient achieved complete remission, 2 patients had rejection, 3 patients had disease progression, and 1 patient had multiple organ failure [23]. Friend et al. reported 2 patients with recurrent hepatocellular carcinoma after liver transplantation developed irreversible acute liver rejection soon after starting nivolumab treatment and eventually died. To sum up, the above findings seem to suggest that nivolumab therapy after liver transplantation has potential clinical benefits but is prone to immune rejection [24].

Shi et al.reported 4 patients with HCC treated with toripalimab after liver transplantation for hepatocellular carcinoma, one with progressive disease and one with stable disease. None of the four patients had rejection [25]. Tsung et al.reported 2 patients with HCC treated with cemiplimab after liver transplantation for hepatocellular carcinoma, and the immunosuppressive drug was tacrolimus. Both patients had no rejection and 1 patient had a partial response [26]. pandey et al. reported a 65-year-old female patient who was treated with ipliumumab after liver transplantation, the immunosuppressive drugs were tacrolimus and everolimus, the patient completely responded and without rejection. The time interval between liver transplantation and ICIs use was 7.2years [27]. Anugwon et al. reported a 62-year-old male patient who was treated with ipliumumab after liver transplantation, the immunosuppressive drug was tacrolimus, however, the patient finally disease progressed and also developed graft rejection. The time interval between liver transplantation and ICIs use was 5years [28]. Rammohan et al. reported a 57-year-old male patient who was treated with pembrolizumab after liver transplantation for liver cancer, the immunosuppressive drugs were tacrolimus and everolimus, the patient partially responded and without rejection. The time interval between liver transplantation and ICIs use was 4.4years [29]. varkaris et al. reported a 70-year-old male patient who was treated with pembrolizumab after liver transplantation for liver cancer, the immunosuppressive drug was tacrolimus. the patient have no rejection, but disease progressed. The time interval between liver transplantation and ICIs use was 8years [30]. De Toni et al. reported a 41-year-old male patient who was treated with Nivolumab after liver transplantation for liver cancer, the immunosuppressive drugs was tacrolimus and, the patient partially responded and without rejection. The time interval between liver transplantation and ICIs use was 1year [31].

Rita et al. reported a case of hepatocellular carcinoma with melanoma metastasis after liver transplantation. After the fourth injection of Ipilimumab, re-examination of CT revealed that the lung and liver tumors had regressed significantly. At the same time, the patient felt good and did not experience rejection or other adverse reactions [32]. Harsha et al. reported a 59-year-old female patient with unresectable melanoma after hepatocellular carcinoma liver transplantation. Treated with ipilimumab, and the immunosuppressive drug was tacrolimus (1.8–3.1ng/mL), there was no rejection reaction and other adverse reactions such as diarrhea, rash, breathing pain, fever, etc., but no effective treatment effect was obtained [33].

In summary, the probability of rejection was 24% (6/25) when ICIs were used after liver transplantation for hepatocellular carcinoma (Table 2), which also raises the question of the safety of ICIs in the management of HCC progression after LT.

Table 2: Characteristics of the patients receiving ICI after liver transplantation.

Year	Author	Age	Sex	ICI	Immunosuppresion drugs	Duration	response	Time between LT and ICI	rejection	last status
2021	Tsung	75	M	cemiplimab	tacrolimus	N/A	N/A	N/A	No	Death
		77	M	cemiplimab	tacrolimus+steroid	12cycle	PR	N/A	No	Death
2020	Jarroudi	70	M	Nivolumab	tacrolimus	4cycle	N/A	3Y	Yes	Death
		62	F	Nivolumab	tacrolimus	5cycle	PD	2.5Y	No	alive
		66	M	Nivolumab	tacrolimus	6cycle	PD	5Y	No	alive
2020	shi	46	M	toripalimab	N/A	7cycle	PD	N/A	No	alive
		46	M	toripalimab	N/A	3cycle	SD	N/A	NO	alive
		62	M	toripalimab	N/A	2cycle	N/A	N/A	NO	alive
		66	M	toripalimab	N/A	single use	N/A	N/A	NO	alive
2020	pandey	65	F	ipliumumab	tacrolimus+everolimus	7cycle	CR	7.2Y	NO	alive
2020	Anugwon	62	M	ipliumumab	tacrolimus	N/A	PD	5Y	Yes	Death
2019	Amjad	62	M	Nivolumab	tacrolimus+MMF	20month	CR	1.3Y	NO	alive
2018	Gassmann	53	F	Nivolumab	tacrolimus+MMF+everolimus	1cycle	N/A	2Y	Yes	Death
2018	Deleon	56	M	Nivolumab	tacrolimus	1.2month	PD	2.7Y	No	Death
		55	M	Nivolumab	sirolimus+MMF	1.1month	PD	7.8Y	NO	Death
		34	F	Nivolumab	tacrolimus	1.3month	PD	3.7Y	NO	Death
		63	M	Nivolumab	tacrolimus	0.3month	N/A	1.2Y	NO	Death
		68	M	Nivolumab	sirolimus	0.9month	N/A	1.1Y	Yes	Death
2018	Rammohan	57	M	pembrolizumab	tacrolimus+everolimus	N/A	PR	4.4Y	NO	alive
2017	Friend	20	M	Nivolumab	sirolimus	2cycle	N/A	3Y	Yes	Death
		14	M	Nivolumab	tacrolimus	2cycle	N/A	3Y	Yes	Death
2017	varkaris	70	M	pembrolizumab	tacrolimus	3month	PD	8Y	NO	Death
2017	De Toni	41	M	Nivolumab	tacrolimus	N/A	PR	1Y	NO	Death
2015	Rita	67	M	ipliumumab	tacrolimus+MMF	3month	PR	8Y	NO	alive
2015	Harsha	59	F	ipliumumab	tacrolimus	2month	SD	8Y	NO	alive

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; N/A, not available
M, male; F, female; Y, year; MMF, Mycophenolate Mofetil

7. Possible Factors for Rejection after the Application of ICIs

Transplant rejection is an important indicator to measure the efficacy and adverse reactions of immune checkpoint inhibitors after liver transplantation. In various transplants, the rejection rate of kidney transplantation was the highest at 41%, followed by liver transplantation at 35% and heart transplantation at 20%. However, the mechanism of rejection by blocking CTLA-4 and PD-1/PD-L1 pathways after liver transplantation is still unclear. Juliya, Fisher et al. found that the rejection rate of nivolumab was the highest in ICIs at 52.2%, followed by pembrolizumab at 26.7% and ipilimumab at 25% [34]. It is reported that CTLA-4 blockers may have a lower risk of causing rejection than PD-1 blockers [35]. According to the analysis of the existing research results, the possible factors for rejection after the application of ICIs are as follows:

7.1. Insufficient use of Immunosuppressive Drugs

In order to achieve the ideal liver transplantation effect, the application of immunosuppressive agents after surgery is crucial, and the effects of immunosuppressive drugs and ICIs interact with each other. A retrospective cohort study included 7 patients with metastatic cancer who were treated with PD-1 inhibitors after liver transplantation. Early rejection was observed in 2 of the 7 patients, and the median time of rejection was 24 days. The researchers analyzed the results and found that transplant patients who had a rejection reaction only used a lower dose of prednisone in the initial stage, and insufficient immunosuppression may lead to graft rejection [23]. For patients after liver transplantation, prednisone alone is not sufficient when starting ICIs treatment. found

that combined immunotherapy based on sirolimus can reduce the level of FoxP3-positive Treg cells in hepatocellular carcinoma liver transplant recipients, and reduce the secretion of IL-10 and TGF-β without increasing rejection, performing safe and effective in clinical application. When transplantation patients start ICIs treatment, using a sufficient amount of tacrolimus is combined with immunosuppressive drugs can reduce the probability of rejection in patients [36]. It can be seen that a sufficient amount of immunosuppressive drugs is necessary to reduce the occurrence of rejection after the application of ICIs. However, how to use immunosuppressive drugs and what is the relationship between the dose of immunosuppressive drugs and ICIs need to be confirmed by further clinical studies.

7.2. Too short Interval between ICIs Treatment and Liver Transplantation

When applying ICIs during the perioperative period of liver transplantation, if the interval between the treatment time and the liver transplantation operation is too short, acute rejection may be induced. Graft rejection occurs earlier than most other autoimmune adverse events, and usually peaks 6-14 weeks after the start of ICI treatment. The median time from treatment initiation to rejection mentioned in previous case reports is 8 days (range: 5-63 days) [37]. In a study by DeLeon et al., liver transplant rejection occurred in patients who received ICI at an interval of 1.1 years after liver transplantation, but liver transplant rejection was not observed in patients who received ICI at an interval of 7.8 years [21]. Existing evidence shows that for patients with a long interval from liver transplantation to the start of ICI treatment, the risk of graft rejection induced by ICIs can be minimized. It is worth noting that close follow-up should be carried out during the first-line routine treatment to identify signs of disease progression early. Moreover, once the disease progresses, the decision to initiate ICI treatment should be made in time to prolong the efficacy of ICI as soon as possible.

7.3. Graft Versus Host Disease (GVHD)

Graft Versus Host Disease (GVHD) is a systemic disease in which the immunocompetent cells of the organ donor recognize the recipient's antigen and produce an immune response, and attack the recipient's target tissues and organs. The mechanism of the occurrence and development of GVHD after liver transplantation is still unclear. The current theories are based on the research experience of Hematopoietic Stem Cell Transplantation (HSCT). Herbaux et al. reported that 6 patients with a history of graft-versus-host disease suffered rejection after receiving ICIs [38]. Haverkos et al. reported that 17 patients had a history of graft-versus-host disease and after receiving ICIs treatment, 12 patients experienced rejection [39]. Once GVHD occurs, it reflects that the recipient is in an over-suppressed state of immune function, so the application of ICIs to such patients should be handled with caution.

7.4. Changes of the Immune Microenvironment

Whether the immune checkpoint regulator found in liver biopsy is related to the occurrence of graft rejection. Munker et al. evaluated 3 available biopsies in liver transplant recipients who had acute transplant rejection using ICIs. The results showed that all patients had elevated PD-L1 expression, while the 4 biopsies of patients without rejection had no positive staining of PD-L1, strongly supports that the expression of PD-L1 can predict graft rejection [40]. In another study, the researchers collected allogeneic liver tissue and tumor tissue pathological specimens and performed PD-L1 staining of patients, and analyzed the expression of PD-L1 in tumor infiltrating lymphocytes (TIL) at the same time. The results indicated that all patients in the cohort PD-L1 expression can be detected in allogeneic lymphocytes in cases of transplant rejection [21]. Therefore, it is further speculated that the level of PD-L1 expression may be used to predict whether patients will undergo rejection after treatment with ICIs, and the high expression of PD-L1 may indicate the occurrence of rejection. And tumor necrosis factor (TNF)-α can directly increase the mRNA and protein levels of PD-L1, thereby promoting immune escape. IL-6 and IL-17 also regulate the expression of PD-L1 through JAK/STAT3 and NF-κB signaling pathways, respectively. Growth factors such as EGF, TGF-β, and GM-CSF can also induce the expression of PD-L1 and promote the occurrence of immunosuppression [41]. Therefore, changes in the microenvironment of tumor inflammatory factors may be involved in the occurrence of ICIs-related rejection in patients with liver transplantation.

8. Conclusions

In summary, the use of ICIs before and after liver transplantation for hepatocellular carcinoma has a certain clinical effect, but we still need to be highly vigilant for the rejection caused by treatment. The interval between immunosuppressive drug treatment and transplant surgery, whether the patient has the history of GVHD, and the patient's immune microenvironment changes can all be used as early warning indicators for transplant rejection. It is recommended that liver transplantation recipients undergo routine liver biopsy before starting ICI treatment, and PD-L1 staining as well as TIL should be considered to evaluate the safety and effectiveness of ICIs treatment. More clinical trials and research are still needed to explore more individualized treatment options.

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