Concensus Statement

**Chinese expert consensus on the application of immune checkpoint inhibitors in liver transplantation for hepatocellular carcinoma**

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**Abstract**

Hepatocellular carcinoma, the most prevalent malignant liver tumor, is typically characterized by a low early detection rate and a poor 5-year overall survival rate. Liver transplantation represents a curative approach for this condition. The emergence and advancements of immune checkpoint inhibitors in the perioperative application of liver transplantation for hepatocellular carcinoma, particularly as an adjuvant therapy for preoperative downstaging/bridging and postoperative tumor recurrence, have raised significant clinical and scientific considerations that warrant further attention and consolidation. This article presents the consensus statement put forward by experts from the Organ Transplantation Branch of the Chinese Medical Association, Liver Transplantation Group of the Organ Transplantation Branch of the Chinese Medical Doctor Association, and the Organ Transplantation Rehabilitation Committee of the Chinese Rehabilitation Medicine Association, drawing from existing literature and their clinical experiences.

**Keywords:** Hepatocellular carcinoma; Immune checkpoint inhibitor; Liver transplantation; Immunotherapy; Rejection

Primary liver cancer (PLC) is the fourth-most common malignancy and second leading cause of tumor-related deaths in China. The prognosis of PLC is poor, with a 5-year overall survival (OS) rate of 14% in patients, which seriously endangers people’s life and health.[1,2] Hepatocellular carcinoma (HCC) accounts for 75–85% of PLCs, and intrahepatic cholangiocarcinoma accounts for 10–15%. At present, radical surgery remains the most effective treatment option for HCC, including liver resection and liver transplantation (LT). Liver resection is recommended for patients with HCC in stages 0 and A of Barcelona Clinic Liver Cancer staging, and in stages I and II of China Liver Cancer staging. LT is recommended for patients with early HCC and concurrent cirrhosis, liver dysfunction, and a poor physical condition.[1,3,4] The indications of LT for HCC are relatively strict because of a shortage of donor livers and the risk of postoperative tumor recurrence and metastasis. Internationally recognized criteria include the Milan criteria proposed by Professor Mazzaferro in 1996, UCSF criteria, up-to-seven criteria, Kyoto criteria, and Hangzhou criteria. These criteria can almost achieve a 5-year OS rate of >70%.[5] During the waiting donor period, patients with HCC who meet these LT criteria need to receive some treatment to avoid withdrawing from the waiting list because of tumor progression. This situation is called bridging treatment. In patients with HCC who exceed the LT criteria at the initial diagnosis, regional and systematic treatment can be adopted. This treatment reduces the tumor burden and tumor marker levels and enables patients to meet the LT criteria, which is called downstaging treatment. In recent years, new drugs for HCC have been continuously developed at home and abroad. Among them, systemic therapeutic drugs represented by molecular targeted drugs and immune checkpoint inhibitors (ICIs) have created a new era in the treatment of HCC and have become the main treatment modes for unresectable HCC.[6,7] Bridging or downstaging treatment before LT could refer to current strategies and models of neoadjuvant therapy or conversion therapy for HCC. After LT, the main problems are tumor recurrence and metastasis for recipients. Previous studies showed that the 5-year tumor recurrence rate after LT was 20.0–57.8%, and the most common recurrence occurred in the lungs, liver, abdominal cavity, and bone. The median survival time of recipients after HCC recurrence was only 12.9 months.[8–10] Various regional treatments, such as ablation, intervention, and radiation therapy, can be adopted for tumor recurrence and metastasis after LT. Systemic treatment, such as targeted drugs and chemotherapy, is also used in clinical practice. However, there is still some controversy regarding the application of ICIs for preventing or treating tumor recurrence and metastasis. Currently, there is significant absence of standardized guidelines or widespread consensus on the application of ICIs in LT for HCC among both domestic and international medical communities. To achieve effective and safe application of ICIs for patients with HCC before and after LT, in August 2023, the Organ Transplantation Branch of the Chinese Medical Association convened national experts to jointly formulate the “Expert Consensus on Application of Immune Checkpoint Inhibitors in Liver Transplantation for HCC Patients” (referred to as the consensus hereafter). This consensus provides scientific guidance and serves as a reference for preoperative and postoperative applications of ICIs for LT recipients with HCC in China. The Levels of Evidence (March 2009) by the Oxford Centre for Evidence-Based Medicine was adopted to grade the quality of evidence and the strength of recommendations for each clinical issue in this consensus[11] [Table 1]. Additionally, anonymous voting was conducted back-to-back among experts from the writing group and the review group. Voting levels were divided into the following: (a) full agreement; (b) basic agreement; (c) uncertain; (d) not quite agree; and (e) completely disagree. If the number of votes for any of a, b, c, or d exceeded 50%, or the number of votes for a + b, c + d exceeded 70%, the consensus was considered to have been reached. If these votes did not exceed these percentages, no consensus was considered to have been reached, and relevant opinions proceeded to the next round of voting. The percentage of a + b or d + e votes was used as the expert consensus degree of each recommendation.[12] In view of the low incidence rate of HCC among adolescents and the potential adverse effects of ICIs on this group, this consensus applies only to adult HCC patients aged 18 and above.

**Application of ICIs in the Preoperative Treatment of LT for HCC**

***Indications for the application of ICIs before LT for HCC***

The use of ICIs before LT for HCC is mainly for downstaging/bridging therapy, with the aim of reducing the tumor burden and controlling tumor progression.[13] ICIs can be used in patients with mid- or advanced-stage HCC with good liver function [Table 2] and a good performance status score (1–2 points) and no distant metastasis.[3] In patients with portal vein tumor thrombus (PVTT), there have been case reports of successful application of ICIs in downstaging phase treatment.[14] In the IMbrace150 study, a subgroup analysis of large-vessel invasion showed that progression-free survival (PFS) and OS were beneficial after treatment with atezolizumab combined with bevacizumab.[15] However, VP4 type, median overall survival (mOS) only lasted for 7.6 months, with an increased incidence of variceal bleeding and gastrointestinal bleeding.

**Recommendation 1: Pre-LT ICIs for HCC are mainly suitable for patients with mid- or advanced-stage HCC, without distant metastasis, and with good liver function and physical fitness scores. Fully informing patients and obtaining informed consent before treatment are necessary because of the lack of high-level evidence for ICIs in the pre-treatment of LT for HCC (recommendation strength C; evidence level 4; expert consensus: 100%).**

***Contraindications for using ICIs before LT for HCC***

The Chinese Multidisciplinary Expert Consensus on Immunotherapy Combined with Hepatocellular Cancer (2023 Edition)[7] and expert opinions indicate that there are no absolute contraindications for using ICIs before LT for HCC. However, caution should be exercised in the following situations. (1) Patients with autoimmune diseases, such as myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus, and erythematosus are not recommended to use ICIs. (2) Untreated or incompletely treated patients with gastric varices accompanied by bleeding or at high risk of bleeding should undergo esophagogastroduodenoscopy to evaluate the condition of gastric varices before using immunotherapy combined with anti-angiogenesis therapy, and pre-treatment must be performed according to the diagnosis criteria. ICIs can be used only after the condition stabilizes. (3) Patients with idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonia, or idiopathic pneumonia, or those with evidence of active pneumonia on recent chest computed tomography (CT) images should use ICIs with caution. (4) Among patients who have major cardiovascular and cerebrovascular diseases (e.g., New York Heart Association grade II or more serious heart disease, myocardial infarction, and cerebrovascular accident within 3 months before starting treatment) and those with unstable arrhythmias or unstable angina pectoris should use ICIs with caution. (5) Patients with moderate-to-severe ascites and severe infections are advised to undergo treatment before using ICIs.[7]

**Recommendation 2: Before ICI treatment, careful evaluation of contraindications should be performed. Caution should be exercised in the following situations: (1) patients with autoimmune diseases, (2) patients with gastric varicose veins accompanied by bleeding or high risk of bleeding, (3) patients with idiopathic pulmonary fibrosis or pneumonia, (4) patients with major cardiovascular disease or unstable arrhythmias, and (5) patients with moderate-to-severe ascites or severe infections. The above-mentioned opinions are mainly based on clinical experience in mid- to advanced-stage HCC. Therefore, more clinical research evidence on LT for HCC is required to support these opinions (recommendation strength C; evidence level 4; expert consensus: 95.8%).**

***Pre-transplant ICIs for patients with HCC***

ICIs have been used for pre-transplant downstaging/bridging therapy and mainly include PD-1/PD-L1 monoclonal antibodies and CTLA-4 monoclonal antibodies. Commonly used monoclonal antibodies include nivolumab, pembrolizumab, camrelizumab, atezolizumab, sintilimab, toripalimab, and ipilimumab.[16–18] The main ICI used in pre-transplant downstaging/bridging therapy is nivolumab (100–240 mg/2 weeks, 1–34 cycles).[12,17]

**Recommendation 3: On the basis of published case reports and clinical experience, ICI monotherapy can be safely used before transplantation (recommendation strength C, evidence level 4; expert consensus: 87.5%).**

***Pre-transplant ICI combination treatment regimen for HCC***

The use of ICIs before LT for HCC is often combined with other treatments, such as transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), radiofrequency ablation, radiotherapy, and targeted therapy.[8,16] Choosing a suitable combination treatment regimen on the basis of individual conditions is necessary. The combination of ICIs, TACE, and/or molecular targeted drugs is still a new treatment option that requires multicenter, large-scale, clinical validation. At present, the combination of multiple treatments is believed to achieve better downstaging efficacy than monotherapy.[9,10]

A first-line ICI combination treatment regimen before transplantation specifically includes the following: (1) ICIs combined with antiangiogenic drugs; (2) ICIs combined with tyrosine kinase inhibitors (TKIs); (3) dual ICI combination therapy; and (4) systemic therapy combined with local regional therapy.

1. ICIs combined with antiangiogenic drugs: The international multicenter phase III clinical trial IMbrave150 reported a median OS of 19.2 months for atezolizumab combined with bevacizumab, a median disease PFS of 6.9 months, and an objective response rate (ORR) of 30%.[14] This combination had a greater therapeutic advantage in the Chinese subgroup population, with a median OS of 24.0 months. At present, this treatment regimen is recommended as a priority for first-line treatment by various academic societies and guidelines.[1,3,7] Recent case reports have also confirmed the successful application of this treatment regimen in pre-transplant downstaging treatment for patients with HCC.[13]
2. ICIs combined with TKIs: Several studies have shown good anti-tumor effects of ICIs combined with TKIs as first-line treatment. This treatment was recommended as a first-line treatment by the Chinese Society of Clinical Oncology in 2022, and it includes apatinib combined with camrelizumab, and lenvatinib combined with nivolumab or pembrolizumab was taken as an alternative treatment.[7]
3. Dual ICI combination therapy: Durvalumab combined with tremelimumab for dual immunotherapy was recommended by the Chinese Society of Clinical Oncology in 2022 as a grade I expert recommendation for patients with advanced HCC.[7]
4. Systemic therapy combined with local regional therapy: Local regional therapy combined with systemic therapy, such as immunotherapy and targeted therapy, can further improve anti-tumor efficacy. Multiple guidelines recommend systemic therapy combined with local regional therapy as first-line treatment.[1,3] Prospective studies based on ICIs combined with local regional treatment are currently underway.

There is still few evidence from large-scale, phase III clinical trials for clear recommendations on the selection of second-line and third-line treatment regimens. Based on the progression of HCC and the specific composition of first-line and second-line treatment regimens, individualized selection of these treatment regimens should be made according to the synergistic mechanism of different treatment methods under a multidisciplinary diagnosis and treatment (MDT) team.

**Recommendation 4: The combination of ICIs and multiple treatments (e.g., TACE, radiofrequency ablation, radiotherapy, and targeted therapy) can achieve better therapeutic effects than monotherapy, but the appropriate combination treatment regimen needs to be selected according to individual conditions (recommendation strength C, evidence level 4; expert consensus: 100%).**

**Recommendation 5: The current first-line treatment regimens for ICIs combination therapy should include atezolizumab combined with bevacizumab, sintilimab combined with bevacizumab analogs, and apatinib combined with camrelizumab. If first-line treatment regimens are ineffective, second-line and third-line regimens may be considered (recommendation strength A; evidence level 2a; expert consensus: 100%).**

***Evaluation of therapeutic effect of ICI application before LT in patients with HCC***

The efficacy of preoperative ICIs in LT for HCC can generally be comprehensively evaluated using contrast-enhanced CT and magnetic resonance imaging (MRI) combined with tumor markers, such as alpha-fetoprotein and abnormal prothrombin. To accurately reflect the changes in tumor density, necrosis, and other factors after ICI treatment, imaging evaluation can use the modified response evaluation criteria in solid tumors (mRECIST). The mRECIST evaluate the target lesion with enhanced CT or MRI arterial phase uptake of a contrast agent, which can avoid underestimating the efficacy.[19] In LT recipients beyond the criteria of transplantation, the ideal therapeutic effect of ICIs is to successfully downstage to meet the transplant criteria. A retrospective cohort study from China included 16 recipients who received PD-1 inhibitors before transplantation. Most (93.7%) patients had a complete or partial response after treatment, and four recipients exceeded the transplant criteria at diagnosis and successfully downgraded after treatment.[20] This finding indicates that ICIs have a certain effectiveness as a downstaging treatment. A clinical study with a larger sample size is required to verify the success rate of ICI treatment before LT and determine whether there is an improvement in the prognosis after successful downstaging. However, according to a multicenter, clinical study in China, recipients who successfully downgraded to the Hangzhou criteria achieved the same prognosis as those who initially met the criteria.[21]

**Recommendation 6: Dynamic enhanced MRI or CT should be used as imaging examinations in combination with tumor markers, such as alpha-fetoprotein and PIVKA-II, for evaluating the efficacy. The mRECIST can be used for imaging evaluation. Follow-up imaging should be performed every 6–8 weeks for the first 6 months after starting ICI treatment and may be combined with tumor markers for follow-up every 9–12 weeks (recommendation strength C, evidence level 4; expert consensus: 100%).**

**Recommendation 7: In liver transplant recipients who have exceeded the criteria for HCC and those who successfully downstage to the Hangzhou criteria can achieve a similar prognosis to that in those who initially meet the criteria (recommendation strength B, evidence level 2a; expert consensus: 95.8%).**

***Interval between discontinuation of ICIs and transplantation before LT for HCC***

Pre-transplantation ICI treatment may induce rejection reactions after transplantation, which is one of the most important factors determining the time between discontinuation and transplantation. The common half-life of ICIs is shown in Table 2. An example of this time is that, when taking Nivolumab, although its half-life is 28 days, its effect on lymphocytes can still be observed after its discontinuation 85 days later.[22] Therefore, guiding the interval from discontinuation to transplantation solely based on the half-life of the drug is not possible. In addition, prolonged discontinuation of treatment results in an extended waiting time for transplant recipients and an increased risk of HCC progression and complications, which may result in patients losing the opportunity for transplantation. According to the literature, the probability of acute rejection in LT for HCC recipients who have received ICI treatment before transplantation is 37% (20/54), and the probability of death due to rejection is 5.6% (3/54). The preoperative discontinuation time for acute rejection cases ranges from 8 days to 93 days, and the discontinuation time for most recipients ranges from 30 days to 40 days.[23] Therefore, whether the risk of rejection is related to a shorter preoperative discontinuation time is unclear. In addition, Kuo *et al*[24] summarized the results of pre-transplant application of nivolumab, pembrolizumab, and atezolizumab (22–27 days) with similar half-lives and found that 1.5 half-lives (42 days) were a safe threshold for avoiding post-transplant rejection reactions. (Table 3)

**Recommendation 8: In the case of good tumor control, the preoperative discontinuation time should be 30 days or longer (recommendation strength B; evidence level 2c; expert consensus: 95.8%)**

***Indications for the application of ICIs for tumor recurrence after LT for HCC***

Tumor recurrence after LT for HCC can be divided into a single lesion and disseminated recurrence with multiple metastases throughout the body. The treatment modes are different for these two types. In single lesions, local therapeutic approaches, such as surgical resection, ablation, intervention, radiotherapy, and a variety of other methods, are used. In contrast, in disseminated recurrence, combination systemic therapy, such as targeted drug therapy and chemotherapy, is required.[25] In recent years, ICIs have also been gradually introduced for systemic treatment of tumor recurrence after LT. Since ICIs are not a routine treatment option for tumor recurrence after LT, most of the published data are from case reports, case series, or systematic evaluations.[26–28] Treatment with ICIs is associated with the risk of rejection and even death. Therefore, ICIs are almost never chosen as the treatment of choice for tumor recurrence after LT. In clinical practice, most of the patients with tumor recurrence after LT experience various treatment modalities, such as radiofrequency ablation, surgical resection, interventional therapy, radiation therapy, yttrium 90 microspheres, TKI drugs, anti-angiogenic drugs, and systemic chemotherapy, before applying ICIs. ICIs are often used in cases where the tumor is not effectively controlled after systemic treatment with local therapy and targeted agents. A study was performed in six patients with multifocal tumor recurrence after LT for HCC, whose tumors continued to progress despite several different types of treatment regimens.[29] ICIs were ultimately adopted as the salvage therapy, and three of them received ICIs for stable tumor control. In conclusion, the current use of ICIs for tumor recurrence after LT is mostly single-agent salvage therapy.[30]

**Recommendation 9: ICIs may be used as salvage therapy for patients with recurrent liver cancer after LT when the recurrent tumor continues to progress after receiving several different types of treatment regimens (recommendation strength C; evidence level 4; expert consensus: 91.7%).**

***Contraindications for the use of ICIs in recurrence and metastasis after LT for HCC***

The standard contraindications for the use of ICIs after LT are essentially the same as those before surgery, and thus the preoperative contraindication recommendations can be used. A specific contraindication for the use of ICIs after LT is PD-L1 expression in the transplanted liver tissue. Numerous Chinese and international studies have indicated that positive PD-L1 expression in transplanted liver tissue may be a risk factor for inducing rejection reactions in recipients treated with anti-PD-1 monoclonal antibodies. A clinical trial involving six liver transplant recipients showed that none of the five patients with negative PD-L1 expression in their grafts experienced rejection reactions.[31] However, one patient with positive PD-L1 expression in their graft experienced a rejection reaction. Munker and De Toni,[32] among others, found that liver biopsy tissue was stained positive for PD-L1 in recipients who experienced acute rejection reactions after treatment with ICIs, whereas specimens from recipients who did not experience rejection reactions were negative. Additionally, Nordness *et al*[33] and Chen *et al* [34] reported that PD-L1 was negatively expressed in donor liver tissues before transplantation but positively expressed after transplantation. This finding indicates that PD-L1 is weakly expressed or not expressed in donor liver tissues before transplantation, but its expression increases after reperfusion. This increase may be related to ischemia–reperfusion and could also be a result of acute rejection reactions.[35] Because of individual differences in ischemia–reperfusion injury, preoperative PD-L1 testing on the donor liver cannot fully reflect the real expression of PD-L1 in the liver after transplantation. Therefore, patients with tumor recurrence after LT are recommended to undergo a liver biopsy to examine PD-L1 expression levels, and those with high expression should be contraindicated for PD-1/PD-L1 inhibitors. Being in the acute rejection phase of the graft is a contraindication for the use of ICIs. Two-third of organ transplant recipients with a history of acute rejection reactions experience acute rejection reactions after ICI treatment.[26]

**Recommendation 10: In patients with tumor recurrence after LT, contraindications for the use of ICIs can be the same as those for preoperative contraindications, with a special contraindication that recipients are recommended to undergo a liver tissue biopsy before ICI treatment. Those with positive PD-L1 expression should be contraindicated for PD-1/PD-L1 inhibitors. Being in the acute rejection phase is also a contraindication for the use of ICIs (recommendation strength B, evidence level 3b; expert consensus: 95.8%).**

***Is ICI prophylactic therapy necessary after LT for HCC?***

Currently, all registration trials of ICIs approved for the treatment of HCC have excluded LT recipients. Therefore, the majority of data on post-liver transplant HCC immunotherapy are from case reports and case series studies. ICIs play a role in the immune tolerance required for allograft survival. Therefore, the use of ICIs in LT recipients may trigger allograft rejection. The use of ICIs should be considered as a “last resort.”[36] Despite the risks associated with immunotherapy, it can be used as salvage therapy if existing treatment options do not prolong survival. Recently, a meta-analysis concluded and analyzed 31 reports with a total of 52 LT recipients treated with ICIs. This analysis showed an ORR of 34.6% and a disease control rate (DCR) of 44.2%, acute rejection occurred in 15 (28.8%) patients, and 7 (13.4%) patients died owing to graft loss.[28]

**Recommendation 11: Currently, there is a lack of research on the use of ICIs for preventing HCC recurrence after LT. Because of the risk of triggering rejection reactions, using ICIs as a treatment for preventing tumor recurrence post-LT is not recommended (recommendation strength D; evidence level 5; expert consensus: 95.8%).**

***Treatment strategies of ICIs for recurrence and metastasis of HCC after LT***

ICIs combined with anti-angiogenic drugs

A previous study examined the use of nivolumab in combination with bevacizumab as second-line therapy for recurrent and metastatic liver cancer after transplantation. This study showed that the OS was 26.5 ± 10.4 months in the nivolumab plus bevacizumab group compared with 9.5 ± 5.5 months in the regorafenib group (*P* = 0.02). The main adverse reactions in the immunotherapy group were elevated alanine aminotransferase concentrations and proteinuria.[37] Another conceptual validation study demonstrated that the combination of nivolumab and bevacizumab achieved disease stability with good tolerability and minimal side effects throughout the treatment period.[38] Additional case reports and individual analyses have further supported the efficacy and safety of combining nivolumab with bevacizumab.[39,40]

ICIs combined with TKIs

In the treatment of recurrent and metastatic liver cancer after transplantation with ICIs, most patients have already received multiple TKIs, but there is limited research on the use of ICIs in combination with TKIs. A case report showed that the use of low-dose nivolumab in combination with lenvatinib prevented the recurrence of HCC after LT.[41] The combination of TKIs with immunotherapy can be considered as a treatment option, with the choice of TKI based on previous treatment regimens.

Dual immunotherapy with ICIs

According to the 2022 Chinese Society of Clinical Oncology Liver Cancer Guidelines HIMALAYA study, durvalumab (PD-L1 inhibitor) combined with tremelimumab (CTLA-4 inhibitor) is recommended as a first-line treatment by experts. Clinical studies on dual immunotherapy with PD1 inhibitors combined with CTLA-4 inhibitors (e.g., sintilimab + IBI310; nivolumab + ipilimumab) are also currently being performed.[7] However, due to concerns regarding graft rejection, dual immunotherapy is rarely used for recurrence and metastasis after LT. A case report showed that a patient treated with nivolumab in combination with atezolizumab did not experience rejection reactions and had stable tumor control.[42] Another literature review suggested that the combination therapy of pembrolizumab and ipilimumab has a strong risk of graft rejection compared with monotherapy, and dual immunotherapy is not recommended.[43]

ICIs combined with chemotherapy

Currently, there is a lack of systematic research or reports on the use of ICIs combined with FOLFOX/XELOX therapy, and there is a lack of high-level clinical research evidence to recommend specific protocols. Individualized drug selection and exploratory research based on the patient’s condition are recommended.

**Recommendation 12: The use of ICIs for recurrent and metastatic HCC after LT should mostly be used as salvage therapy, with monotherapy ICIs as the main approach (recommendation strength B; evidence level 2a). Systemic combination options should include combination with bevacizumab (recommendation strength B; evidence level 2b) and combination with TKIs such as lenvatinib (recommendation strength D, evidence level 4), and dual immunotherapy is not recommended (recommendation strength C; evidence level 4; expert consensus: 100%).**

ICIs combined with local therapy

Local therapy, such as surgical resection, radiofrequency ablation, interventional therapy, and radiation therapy, is an important component of HCC treatment. Numerous studies have shown that combining local therapy with systemic treatment can prolong patients’ survival and improve the quality of life.[44] However, there is a lack of systemic research and reports on the combination of ICIs with local therapy in patients with recurrent and metastatic HCC after transplantation, and clear recommendations are lacking. The progression of liver cancer varies among individuals, and a rational choice of local treatment should be made on the basis of efficacy evidence, safety, and tolerability. Although there is a risk of graft rejection with ICI treatment, previous studies have shown that patients with recurrent and metastatic HCC after transplantation should not be preemptively excluded from using ICIs.[28] In the real world, combination therapy with ICIs is complex, with different combinations and sequences of drugs. Therefore, further prospective, clinical studies are required on immunotherapy combinations.

**Recommendation 13: In recurrent and metastatic HCC after LT, ICIs can be combined with local treatment options, such as radiofrequency ablation, TACE, hepatic arterial infusion chemotherapy, and radiation therapy. However, there is currently limited relevant literature and research on combination treatments, leading to insufficient evidence (recommendation strength D; evidence level 5; expert consensus: 95.8%).**

***Evaluation of therapeutic effects of ICI treatment for recurrence and metastasis of HCC after LT***

The evaluation indicators for the efficacy of ICIs in the treatment of recurrence and metastases of HCC after LT are similar to those of neoadjuvant therapy for HCC. The commonly used indicators in clinical trials of ICIs for treating HCC include ORR, PFS, time to tumor progression (TTP), and OS. These indicators were routinely used in most clinical studies related to immunotherapy for HCC recurrence and metastasis after LT.[45–47] Usually, imaging examinations and tumor markers detection are performed during fixed treatment cycles. Imaging physicians could evaluate tumor regression, necrosis, or progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) and/or mRECIST (modified RECIST), and calculate ORR to reflect treatment outcomes.[48] Meanwhile, the common tumor markers of HCC, such as alpha fetoprotein (AFP) and abnormal prothrombin II (PIVKA-Ⅱ), are also evaluated. For the imaging monitoring of HCC lesions, dynamic enhanced CT and MRI have high clinical applicability. MRI has a higher detection rate for small lesions, especially Gd EOB DTPA enhanced MRI provides a more accurate evaluation for multiple small lesions.[45,49] Therefore, for HCC patients treated with ICIs, dynamic enhanced MRI is preferentially recommended for imaging evaluation.

**Recommendation 14: The main efficacy indicators for immune checkpoint therapy for recurrence and metastasis of HCC after LT can be PFS and overall survival. Secondary efficacy indicators can be the main pathological response, ORR, and time to tumor progression (recommendation strength B; evidence level 2a; expert consensus: 100%).**

***Potential biomarkers for the benefits of ICI treatment in the recurrence and metastasis of HCC after LT***

Previous studies showed that the recurrence of liver cancer after LT is associated with an ORR of approximately 35% when treated with ICIs, while the occurrence rate of rejection reactions is approximately 30%.[26–28] Consequently, preselecting patients who would benefit from ICIs treatment before therapy is crucial to enhance the treatment response rate and minimize the incidence of rejection reactions. Currently, there are many biomarkers associated with treatment benefits for tumor recurrence after liver cancer transplantation. Therefore, we examined pertinent literature reports on biomarkers for ICI treatment benefits in liver cancer. DNA mismatch repair deficiency can lead to microsatellite instability (MSI), a high tumor mutation burden (TMB), and increased neoantigens, which can be used to identify potential biomarkers for immunotherapy benefits in patients with malignant tumors.[50]

1. PD-L1 is a natural ligand of PD-1, which promotes tumor immune escape by inhibiting T lymphocyte activation. The expression level of PD-L1 in tumor tissue can serve as a response marker for PD-1 or PD-L1 monoclonal antibody treatment. Previous studies have shown a certain correlation between PD-L1 expression levels and immune therapy response in HCC[51]: (1) In the KEYNOTE-224 trial, PD-L1 expression calculated by the combined positive score (CPS, cutoff = 1) was found to be associated with improved ORR and PFS in responders (CR/PR), whereas PD-L1 expression calculated by the tumor proportion score (TPS, cutoff = 1%) has no predictive value as CPS. (2) In the CheckMate 459 trial, although patients with baseline PD-L1 expression ≥1% had higher ORR in the nivolumab group (28% *vs*. 12%), no difference was observed in PFS and OS. (3) In summary, PD-L1 has a certain reference value in the immunotherapy of HCC.

2. MSI testing may predict the efficacy of immunotherapy in patients with cancer, and tumors with high microsatellite instability (MSI-H) show superior outcomes in immunotherapy. However, the incidence of MSI-H in patients with HCC is relatively low (approximately 0.8–5% for a TMB >10 mutations/Mb and only 0.2–3% for MSI-H) compared with that of gastric and colon cancer.[52,53] This low incidence restricts the use of MSI testing in immunotherapy for liver cancer.[54]

3. The TMB has been validated in multiple, randomized, phase III studies as a predictor of the efficacy of ICI treatment in patients with cancer. In a randomized, controlled study on non-small cell lung cancer (CheckMate 026), patients with a high TMB (≥243 mutations) showed a longer PFS and a higher ORR with nivolumab monotherapy than with chemotherapy.[55] Another cohort study (CheckMate 227) also showed that, in patients with a TMB ≥10 mutations/Mb, dual immunotherapy was more effective in extending PFS than chemotherapy (7.2 months *vs* 5.5 months).[56] Hill’s study showed that single-agent ICI treatment significantly prolonged the OS compared with chemotherapy in patients with advanced endometrial cancer and an MSI-H/high TMB. Immunohistochemical detection of a high DNA mismatch repair and an MSI-H identified through second-generation sequencing is consistent, with 94.3% of MSI-H cases aligning with TMB ≥10 mutations. Additionally, the results of the next-generation sequencing can better predict the efficacy of ICI treatment.[50] However, the IMbrave150 study showed no significant correlation between the TMB and the response rate or OS in 130 patients with liver cancer.[57] There is a lack of a standardized TMB threshold. Therefore, combining other predictive biomarkers to collectively determine the efficacy of immunotherapy for patients with HCC and recurrent metastatic tumors after LT may be necessary.

4. Tumor-infiltrating lymphocytes (TILs), which encompass lymphocytes that infiltrate tumor tissues from the bloodstream, including T cells, B cells, natural killer cells, and macrophages, represent a vital component of the tumor microenvironment.[58] Several models based on the TIL status have been established to guide immunotherapy for cancer,[59,60] and CD8+ T cell infiltration is considered a prospective prognostic biomarker for liver cancer. Studies have indicated that patients with a high proportion of CD8+ TILs in tumor tissue show a prolonged OS.[61] However, further research is warranted concerning the status of TILs and their combined prediction of rejection reactions with other molecular biomarkers.

5. The neutrophil-to-lymphocyte ratio (NLR) in peripheral blood can effectively reflect the body’s inflammation and immune status.[62] LT recipients with a preoperative NLR ≥5 have a significantly increased risk of liver cancer recurrence after surgery.[63] Choi studied 194 patients with HCC treated with nivolumab and showed that a low NLR (<3) was correlated with longer median OS and PFS compared with a high NLR (≥3).[64] Dharmapuri *et al*[65] studied 103 patients with HCC who were treated with nivolumab. They found that patients with a low NLR (<5) before or after treatment had a significantly prolonged median OS and PFS compared with patients with a high NLR (≥5).

Additionally, immune checkpoint molecules in tumor tissue, such as CTLA-4, LAG3, and IDO1, which show high expression levels, may serve as potential biomarkers for targeted ICI therapy.

**Recommendation 15: Currently, there is a lack of reports on biomarkers indicating the benefits of ICI treatment for postoperative tumor recurrence and metastasis after LT. Regarding biomarkers indicating the benefits of ICI treatment in HCC, biomarkers in tumor genomics (e.g., mismatch repair defects, MSI, and TMB), TIL subsets, and the NLR in peripheral blood may be related to the efficacy of ICIs. High expression of immune checkpoint molecules (such as PD-LI) in tumor tissue is also a potential biomarker for a benefit of ICI treatment (recommendation strength C; evidence level 4; expert consensus: 91.7%).**

***Adjustment of the anti-rejection regimen during ICI treatment for recurrence and metastasis of HCC after LT***

Immunosuppressive agents after LT include four types: steroids, mTOR inhibitors (e.g., sirolimus and everolimus), calcineurin phosphatase inhibitors (CNIs) (e.g., tacrolimus and cyclosporine), and mycophenolate mofetil. Different immunosuppressive agents act at different stages of the cell cycle; therefore, they are often used in combination for optimal results. Theoretically, immunosuppressive therapy may attenuate the effects of ICIs. However, in actual clinical practice, some LT recipients who receive ICIs and immunosuppressive therapy still show a positive response to immunotherapy. Kumar *et al*[26] reported 64 cases of ICI therapy after organ transplantation, including 39 renal transplants, 19 liver transplants, 5 heart transplants, and 1 corneal transplant. They found that the ORR was 36% and the DCR was 45%, which was similar to the non-transplantation population. At the beginning of the study, some centers changed the immunosuppressive regimen to low-dose hormone monotherapy maintenance at the initiation of ICIs to reduce the effect of immunosuppressive therapy on the efficacy of ICIs. This change resulted in a high incidence of acute rejection of 75% (9/12). Further studies showed that the incidence of rejection with tacrolimus monotherapy during ICIs was 10%, and that tacrolimus and a combination regimen did not affect the tumor response.[26] A meta-analysis by Xie *et al* showed that the incidence of rejection also varied among patients receiving different immunosuppressive regimens during treatment with ICIs.[67] The incidence of rejection was higher in patients treated with steroids than in patients treated with other immunosuppressive regimens. The probability of rejection was lower in patients treated with CNIs, which is consistent with the results of a previously published study by Wahab *et al*.[57] This study showed that, among LT recipients treated with ICIs, the rate of graft rejection was 60% (3/5) in patients treated with sirolimus monotherapy, 11% (1/9) in those treated with tacrolimus monotherapy, 40% in those with a two-agent combination regimen, and 0% in those with three- or four-agent combination regimens. Furthermore, the remission rate from ICI treatment was 20% for tacrolimus alone, 20% for sirolimus alone, and 38% for the two-drug combination.[67] The use of combined immunosuppressive regimens may be more helpful in promoting a disease response than single-drug regimens.[68] However, the conclusions are not reliable because of the small number of cases in the groups in these studies.

Sirolimus or everolimus may also be used as the primary anti-rejection agent during treatment with ICIs. Mechanistically, PD-1 monoclonal antibody can activate CD8+ T cells through the PI3K-AKT-mTOR pathway to induce rejection. Sirolimus or everolimus can block this pathway, which not only inhibits tumor growth, but also suppresses immune inflammation.[42] In addition, researchers in China recently found that mTOR inhibitors combined with a PD-L1 monoclonal antibody effectively inhibited TP53 wild-type HCC.[69] Previous studies showed that for the HCC patients after LT who received ICIs treatment, the regimen of mTOR inhibitors combined with CNIs had more benefit with lower incidence of rejection and higher ORR and DCR, which were similar with the non-transplantation population.[42,67,69] It has also been shown that sirolimus combined with a dynamic hormone regimen can also achieve a satisfactory anti-rejection effect. A study showed that methylprednisolone 40 mg/day (for 3 days), methylprednisolone 20 mg/day (for 3 days), and methylprednisolone 10 mg daily thereafter until the end of a cycle of ICIs, with a sirolimus concentration of 4–6 ng/mL, had an anti-rejection effect.[70] Therefore, tacrolimus or sirolimus should be used as the basis of an immunosuppressive regimen during ICI treatment.

**Recommendation 16: An immunosuppressive regimen based on tacrolimus or sirolimus is recommended during treatment with ICIs. Since the incidence of rejection with single-agent immunosuppressive regimens is higher than that with combination immunosuppressive regimens, tacrolimus combined sirolimus was recommended (recommendation strength C, evidence level 4; expert consensus: 95.8%).**

**Management of Adverse Effects of ICIs in LT Recipients for HCC**

***Common adverse events and management***

The administration of ICIs has the potential to induce immune-related adverse events (irAEs) by triggering immune system activation, leading to effects on multiple tissues and organs without specificity.[71] The spectrum of irAEs encompasses the skin, liver, gastrointestinal tract, pancreas, heart, kidneys, lungs, and endocrine system. Various ICIs can provoke a range of irAEs, commonly including rash, dermatitis, fatigue, and gastrointestinal reactions.[72]

Organ-specific irAEs and managements

Skin

Skin-related irAEs encompass drug-induced rashes, inflammatory reactions, blistering drug rashes, reactive cutaneous capillary endothelial proliferation (RCCEP), and severe cutaneous adverse reactions (SCARs).

*Management*: Early-detected and mild skin irAEs can generally be managed symptomatically without impacting the course of ICI treatment. In the case of SCARs with a high mortality rate,[73] it is essential to halt or discontinue ICI treatment permanently. Patients should be administered glucocorticoids and immunosuppressants, and dermatological consultation may be necessary.

Liver

HCC recipients exhibit a higher susceptibility to liver damage than recipients of liver transplants for other diseases when using ICIs, resulting in elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels.[74] The liver damage induced by ICIs is considered an indirect injury to the liver due to enhanced immune function, also known as immune-mediated hepatitis (IMH).

*Management*: Management principles are contingent on the severity of IMH. If it is grade 2 or higher, ICIs should be suspended or discontinued, and patients should receive additional glucocorticoids and immunosuppressants.[75]

Gastrointestinal tract and pancreas

The use of PD-1/PD-L1 antibodies often leads to immune-related colitis and pancreatitis.[76] Immune-related colitis is primarily characterized by diarrhea and abdominal pain, while immune-related pancreatitis is characterized by elevated levels of amylase and lipase, with or without abdominal pain. It is essential to differentiate these conditions from other diseases using relevant imaging.

*Management*: Symptomatic treatments, such as rehydration and anti-diarrheal measures, are recommended for immune-related colitis of grade 2 or less. Corticosteroids are necessary for immune-related colitis of grade 2 or higher, and infliximab or vedolizumab may be added, if needed.[77] Additionally, consideration should be given to discontinuing ICIs.[78] For immune-related pancreatitis of grade 2 or less, temporarily discontinuing ICIs and providing symptomatic treatment are recommended. For patients with pancreatitis of grade 2 or higher, discontinuing ICIs and administering treatment with pancreatic enzyme inhibitors and corticosteroids are advised.

Endocrine system

The endocrine system commonly experiences dysfunctions such as thyroid disorders and hypophysitis,[72] with the former being the most prevalent endocrine irAE, primarily involving hypothyroidism and hyperthyroidism.[79]

*Management*: (1) When thyroid function deteriorates to grades 2–3, ICIs should be temporarily halted, and thyroid hormone supplementation (thyrotropin >10 IU/L) is necessary. In cases of grade 4, emergency intervention with corticosteroid treatment is required, and ICIs should be permanently discontinued. In the presence of severe symptoms of hyperthyroidism (grades 2–3), ICIs should be temporarily suspended, and antithyroid drugs such as methimazole or propylthiouracil should be administered. For life-threatening hyperthyroidism (grade 4), treatment should follow the protocol for thyroid storm, including corticosteroids, and ICIs should be permanently discontinued. (2) In cases of more severe hypophysitis (grades 2–3), consideration should be given to temporarily suspending ICIs and administering corticosteroid treatment. In life-threatening situations (grade 4), emergency intervention with high-dose corticosteroids (2 mg ⋅ kg−1 ⋅ day−1 of prednisone) should be administered, and ICIs discontinued.

Heart

The main manifestation is immune-related myocarditis.[80]

*Management*: In cases of grade 1 elevation in cardiac injury markers, the initiation of ICIs treatment should be reconsidered. If necessary, corticosteroids should be administered after consulting with a cardiologist. In the event of an asymptomatic myocarditis diagnosis, immediate treatment with methylprednisolone at a dose of 1–4 mg ⋅ kg−1 ⋅ day−1 is recommended, followed by a gradual reduction in dosage after 3–5 days. If mild cardiovascular symptoms coexist with cardiac injury markers and/or electrocardiogram abnormalities, prompt cessation of ICIs should be followed by corticosteroid treatment. If needed, immunosuppressants can be considered. For significant symptoms or life-threatening conditions, discontinuation of ICIs is advised. Multidisciplinary consultation, ICU management, and high-dose methylprednisolone shock therapy (500–1000 mg/day), with dosage reduction after 3–5 days, along with circulatory and respiratory support, plasmapheresis, and use of immunosuppressants as necessary, should be initiated.[81]

Kidney: The primary manifestation is acute kidney injury (AKI)

*Management*: In the case of severe renal injury (grade 2), it is recommended to temporarily halt ICIs and initiate corticosteroid treatment. For adverse reactions of grades 3–4, it is advised to permanently cease the use of ICIs and manage with corticosteroids. In certain cases, mycophenolate mofetil may also be considered.[77]

Lungs: Pneumonia associated with immunotherapy is relatively uncommon, but it can lead to severe complications

*Management*: In case of grade 2 immunotherapy-induced pneumonia, it is recommended to cease the use of ICIs and administer systemic corticosteroids. After ensuring there is no infection, empirical anti-infection treatment should be provided. For persistent grade 2 reactions or grades 3–4 reactions, ICIs should be discontinued permanently. Higher doses of corticosteroids should be administered, and if corticosteroid treatment does not show effectiveness within 48–96 h, consideration should be given to treatment with immunosuppressants such as infliximab or mycophenolate mofetil, along with empirical anti-infection treatment if complete exclusion of infection is not possible. Additionally, for patients receiving ≥20 mg/day of corticosteroids or equivalent drugs for ≥4 weeks, prophylaxis for pneumocystis pneumonia is recommended if there are no contraindications.[82]

**Recommendation 17: The predominant adverse effects induced by ICIs are related to the skin and gastrointestinal system. Particular vigilance is necessary in the event of major organ adverse reactions, such as those affecting the liver, lungs, and heart. Mild adverse reactions call for a temporary pause in ICI treatment and symptomatic support, while reactions of grade 2 and above frequently require discontinuation of ICIs. Additionally, if deemed necessary, corticosteroids and immunosuppressive drugs should be added (Recommendation strength B, evidence level 2c; expert consensus: 100%).**

***Diagnosis and management principles of rejection induced by ICIs treatment after LT***

Rejection is a significant complication after LT for HCC treated with ICIs. It is a leading cause of graft loss, primarily due to acute cellular rejection mediated by T cells.[83] The mechanism involves the activation of T lymphocytes and enhanced immune function. The incidence of acute rejection following ICIs treatment for HCC LT varies, typically occurring around 3 weeks after the initial treatment.[43]

Risk factors

Common risk factors for postoperative immunotherapy include the use of PD-1 antibodies,[84] positive PD-L1 expression in the graft liver tissue,[85,86] a short interval between transplantation and immunotherapy,[84] and the type and dosage of immunosuppressive drugs used prior to immunotherapy. Single drug regimen or low doses are associated with a higher likelihood of acute rejection.[26]

Clinical manifestations and diagnosis

The clinical features of acute rejection arising from immunotherapy are not significantly different from those of ordinary acute rejection. Patients may exhibit atypical clinical signs or have symptoms such as fever, irritability, local tenderness in the liver area, jaundice, or progressive deterioration of non-specific signs. Laboratory tests may show persistent elevation in serum bilirubin and transaminases, increased levels of alkaline phosphatase (ALP) and γ-glutamyltransferase (γ-GT), and prolonged prothrombin time. The gold standard for diagnosing acute rejection remains pathological examination.[87] The most distinctive histopathological changes of acute rejection include inflammatory cell infiltration in the portal area, endothelitis, and the “triad” of bile duct damage. This triad consists of: (1) inflammatory cell infiltration in the portal area, predominantly with lymphocytes, as well as varying amounts of neutrophils and eosinophils; (2) subendothelial lymphocytic infiltration in portal and/or central veins; (3) bile duct damage, with inflammatory cell infiltration within the bile duct epithelium, leading to bile duct epithelial cell degeneration and apoptosis. Endothelitis is the most important diagnostic feature, with severe rejection affecting hepatocytes and liver lobules, showing focal necrosis, and even peri-central venous hepatocyte necrosis. Acute rejection is diagnosed clinically based on the 2003 Banff grading criteria, with the “triad” scoring 3 points each, graded according to severity and summed. A score of 0–2 points indicates no rejection, 3 points indicate borderline or suspected rejection, 4–5 points indicate mild rejection, 6–7 points indicate moderate rejection, and 8–9 points indicate severe rejection.[88]

Management principles

ICIs may be administered to patients who have experienced recurrent or neoplasm following HCC LT, often alongside a reduction in immunosuppressive drugs to lower the intensity of immunosuppression. In the event of secondary acute rejection, immediate discontinuation of ICIs is necessary. Mild acute rejection may not require corticosteroid shock therapy; instead, prudent observation and combination medication to bolster immunosuppression, including an increase in the dosage of calcineurin inhibitors, can often alleviate the condition. However, monitoring serum levels of drugs and conducting a liver graft biopsy is essential. Once pathology confirms an easing or disappearance of rejection, timely dosage reduction is crucial to avoid drug toxicity or excessive immunosuppression. In cases of moderate-to-severe acute rejection, intravenous methylprednisolone shock therapy is generally preferred, in conjunction with combined medication for anti-infection and gastrointestinal mucosal protection. Severe rejection that does not respond to corticosteroid shock therapy may require the use of antilymphocyte globulin (ALG), antithymocyte globulin (ATG), or anti-CD3 monoclonal antibodies.[88] Additionally, for combined humoral rejection, intravenous immunoglobulin or plasma exchange can be considered.[89] In situations of irreversible rejection, re-transplantation should be contemplated in alignment with transplant eligibility criteria.

**Recommendation 18: It is crucial to conduct early monitoring of rejection following the use of ICIs in liver transplant recipients, as the clinical manifestations may not have distinct features and therefore require differentiation from immune-related hepatitis. Graft biopsy serves as the gold standard for diagnosis (Recommendation strength B, evidence level 2a; expert consensus: 91.7%).**

**Recommendation 19: The first step in managing rejection secondary to ICIs is to immediately discontinue the use of ICIs. Mild acute rejection may be treated with combined medication to enhance immunosuppression, including increasing CNIs doses. Meanwhile, moderate-to-severe acute rejection may require intravenous methylprednisolone shock therapy. In cases of severe rejection unresponsive to hormone shock therapy, antilymphocyte globulin, antithymocyte globulin, or anti-CD3 monoclonal antibodies can be considered. For combined humoral rejection, options include intravenous immunoglobulin or plasma exchange. In situations of irreversible rejection, re-transplantation should be considered, in conjunction with transplant eligibility criteria. (Recommendation strength B, evidence level 2a; expert consensus: 95.8%).**

***Incidence, prognosis, and high-risk group warning of rejection following ICI treatment after LT for HCC***

Incidence of rejection following ICI treatment after LT for HCC

Recurrence after LT poses a challenge in the choice between immunosupression and anti-tumor immunotherapy. Immunosuppressive drugs may compromise the effectiveness of ICIs, while the use of ICIs may trigger severe graft rejection or even graft loss. Early clinical trials of all ICIs did not include solid organ transplant recipients for these reasons. Studies from both domestic and international sources have indicated that the incidence of rejection following ICIs treatment after LT for HCC ranges from 28% to 54%.[67,86,90–92] De Bruyn *et al*[90] conducted a review of 48 organ transplant patients treated with ICIs, including 19 liver transplant patients, 10 of whom were diagnosed with recurrent HCC, resulting in an overall response rate of 21% and a rejection reaction incidence of 37%. In another study by DeLeon *et al*[86] seven patients who used ICIs after LT recurrence were observed, with two experiencing rejection and one succumbing to multiple organ failure. The PFS and median OS were reported to be 1.1 (0.3–21.1) months and 1.8 (0.7–21.1) months, respectively. Gassmann *et al*[91] studied 29 organ transplant cases using ICIs, among which 13 experienced rejection (45%), with 3 of 11 liver transplant recipients developing rejection (37%), and nivolumab, ipilimumab, and pembrolizumab displaying rejection rates of 56%, 36%, and 33%, respectively. Another investigation reviewed reports of 14 liver transplant recipients treated with ICIs, revealing a rejection incidence of 28%, with the median time for rejection occurrence being 3 weeks after immunotherapy.[92]

Prognosis of rejection following ICI treatment after LT for HCC

Several studies have demonstrated that the prognosis for patients experiencing acute rejection after receiving ICIs is poor, despite aggressive interventions, with mortality rates of 33% and re-transplantation rates of 5.4%.[17,93] Additionally, treatment options for inducing chronic rejection reactions are limited. An investigation conducted by Cui *et al*,[43] revealed an overall mortality rate of 32.1% associated with ICIs, with anti-PD-1 antibodies responsible for 96.3% of death cases. Among the different anti-PD-1 monotherapies, nivolumab exhibited the highest mortality rate at approximately 42.1%, while pembrolizumab showed a lower mortality rate at approximately 22.5%. The mortality rate due to liver transplant rejection was notably high at 71.4%, significantly surpassing other organ transplants.

Furthermore, research by Nguyen *et al*[83] indicated that the severity of complications with anti-PD-1 and anti-PD-L1 drugs was higher compared to anti-CTLA-4 drugs, with liver transplant patients facing a mortality rate of 73.9%, primarily due to liver failure (65.2%). PD-1 inhibitors were found to be associated with a higher risk of rejection and graft loss when compared to CTLA-4 inhibitors.[94,95] In summary, the prognosis for HCC liver transplant recipients who experience rejection following ICIs treatment is considerably poor, especially in comparison to those treated with anti-CTLA-4, and with worse outcomes observed for anti-PD-1 and anti-PD-L1 drugs.

High-risk factors for rejection following ICIs treatment after LT for HCC

The timing of medication post-transplantation significantly affects the risk of rejection, with early use of ICIs posing a high-risk factor.[96,97] Additionally, the dosage of medication is another important consideration, particularly for HCC transplant recipients who often require reduced or discontinued doses of immunosuppressants, thus increasing the risk of rejection.[82] Combination ICI therapy plans are associated with a higher risk of fatal rejection compared to single-drug protocols.[98] Moreover, liver transplant recipients treated with PD-1 inhibitors are more susceptible to rejection than those treated with CTLA-4 inhibitors.[43,71,99] Data reveals that two-third of organ transplant recipients with a history of acute rejection experience similar reactions after ICI treatment.[26] A recent analysis of ICIs treatment after LT showed that the risk of rejection may be related to the time interval between LT and the use of ICIs.[67] It showed a significantly lower incidence of acute rejection when ICI treatment begins in later period, particularly in patients with a median interval of 2–8 years post-transplantation.[86] Pandey and Cohen[100] reported a patient who underwent LT six years after being treated for recurrent liver cancer with ipilimumab. The patient experienced only a temporary rise in liver enzymes and no other irAEs, successfully resolving the recurrent liver cancer. In contrast, the risk of rejection seems to be higher when ipilimumab is used in the early post-transplant period, as evidenced by a patient experiencing graft dysfunction 18 months after transplantation while receiving ipilimumab.[101] Furthermore, other high-risk factors include younger age and increased sensitivity to donor-specific antibodies.[95,102]

**Recommendation 20: The prognosis for rejection after ICIs treatment following liver transplantation for HCC is generally poor. Short interval time post-transplantation and reduced doses of immunosuppressive drugs are significant risk factors for subsequent rejection (Recommendation strength C, evidence level 4; expert consensus: 100%).**

***Preventive strategies for rejection in HCC patients undergoing LT and receiving ICIs treatment***

The population of HCC patients undergoing LT and receiving ICIs is unique due to multiple factors. Firstly, this group often presents with HCC that surpasses the standard criteria for transplantation recipients, such as the Milan or UCSF criteria, at the time of their transplant request. Despite undergoing preoperative downstaging/bridging treatments, the likelihood of recurrence post-transplantation remains notably higher compared to general recipients. Secondly, the administration of ICIs prior to surgery may elevate the risk of post-transplant rejection or even graft loss. Therefore, determining individualized immunosuppressive induction and maintenance protocols post-surgery becomes crucial, considering the recipient’s HCC downstaging efficacy, type and duration of ICI treatment, interval of ICI discontinuation, PD-L1 expression level of the graft, recovery of liver function, and serum concentration of immunosuppressants.[36,83]

Currently, the primary immunosuppressive induction protocol involves methylprednisolone + basiliximab, entailing 500 mg of methylprednisolone during the anhepatic phase, followed by 240 mg on the first postoperative day, gradually decreasing, and 20 mg of basiliximab before and on the fourth day after surgery. Most transplant centers adopt a maintenance immunosuppressive protocol of CNIs + antimetabolite drugs + steroids, typically tacrolimus or cyclosporine + mycophenolate mofetil + methylprednisolone. Due to the significant immunosuppressive capability of CNIs, they are widely utilized in most liver transplant recipients.[93] Studies have demonstrated that low-dose tacrolimus as a minimal immunosuppressive strategy does not heighten the risk of rejection while also avoiding interference with the anti-tumor immune activity of immunotherapy.[103–105] Additionally, due to the anti-tumor properties of mTOR inhibitors, they are often administered to liver transplant patients for HCC. The combination of mTOR inhibitors and low-dose tacrolimus presents a potential alternative strategy worth exploring.[106–108] The impact of additional steroids on immunotherapy efficacy is a subject of debate. While Murakami *et al*[109] reported that steroids could diminish the effectiveness of immunotherapy, some studies on immunotherapy in organ transplant patients suggest that their additional dose may not adversely affect efficacy and could even reduce the risk of irAEs.[104,108]

**Recommendation 21: A personalized immunosuppressive induction and maintenance strategy should be developed considering the downstaging efficacy, the specific type and duration of ICIs treatment, interval for discontinuing ICIs, PD-L1 expression level in the graft, recovery of liver function, and serum concentration of immunosuppressant (Recommendation strength C, evidence level 4; experts consensus: 100%).**

**Role of the MDT Team in ICI Application for HCC Before and After LT**

An MDT team is required to set quality control standards for liver cancer diagnosis and treatment as advocated by the National Cancer Center of China. At present, there is a lack of guidelines or consensus on downstaging treatment before LT or treatment for recurrence after LT. There is still controversy regarding how to arrange and design regional and systemic combination therapy strategies to achieve optimal results. Therefore, cooperation and communication among MDT team members are crucial. This cooperation could ensure timely treatment adjustment according to the condition of the patients and provide personalized best decisions, finally benefiting patients.[110] In patients with HCC, regardless of preoperative or postoperative application of ICIs, they should undergo scientific evaluation and guidance from the MDT team. This guidance includes reviewing indications and contraindications, recommending medication regimens and efficacy evaluations, and monitoring and preventing adverse reactions to ensure the quality of life of patients and maximize their clinical benefits.[7] The MDT team in charge of LT for HCC should be composed of experts from LT or hepatobiliary surgery, oncology, interventional medicine, pathology, radiation therapy, radiology, and pharmacy. MDT team members provide appropriate diagnosis and treatment advice from their professional perspective and choose a scientific treatment regimen based on careful analysis and discussion. Changes in the patient’s condition, treatment outcomes, and adverse reactions should promptly lead to feedback to the MDT team. Real-time evaluation, adjustment of treatment regimens, and timely dealing with adverse reactions should be conducted. Through the accumulation and feedback of cases, the diagnosis and treatment level of the MDT team can be continuously improved. The practice of the MDT management model is not only an international development trend in cancer treatment, but also an important institutional guarantee for effectively implementing standardized HCC treatment and ensuring medical quality and safety.[7,25,110]

**Recommendation 22: In the application of ICIs before and after LT for HCC, an MDT team should be fully involved in the patient’s evaluation, medication regimen, efficacy appraisal, and adverse reaction monitoring and prevention. The MDT model can provide patients with more scientific, reasonable, and comprehensive treatment regimens, and increase their treatment benefits (recommendation strength C; evidence level 4; expert consensus: 100%).**

**Outlook**

Immunotherapy is a new direction that enhances the traditional treatment of HCC. In recent years, drugs represented by ICIs have emerged, and multiple clinical trials in China and internationally have shown that combined ICI treatment considerably improves the treatment effect of HCC. This treatment mode is not only applied for unresectable HCC, but is also used as a reference for preoperative bridging/downgrading treatment and postoperative tumor recurrence for LT recipients. ICI treatment has the potential risk of inducing rejection reactions because of the specificity of organ transplant recipients. Therefore, in LT recipients with HCC, the application of ICIs should be cautious, and the benefits and risks should be comprehensively evaluated. This evaluation is important to reduce the incidence of adverse reactions and rejection reactions in recipients and increase the treatment benefit ratio. In summary, in LT recipients with HCC, the ideal immunotherapy regimen is to only stimulate anti-tumor immunity with minimal adverse reactions and no induction of rejection reactions. However, further research is required on drugs or treatment models with more precise targeting of HCC.

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**Table 1: Grading of evidence for evidence-based medicine.**

|  |  |  |
| --- | --- | --- |
| **Recommended strength** | **Level of evidence** | **Therapy or harm** |
| **A** | 1a | Systematic review of RCTs |
| 1b | RCTs with small confidence intervals for results |
| 1c | Any evidence of an “All-or-none” |
| **B** | 2a | Systematic review of cohort studies |
| 2b | Individual cohort studies (including low-quality RCTs, e.g., those with >20% loss-to-follow-up rates) |
| 2c | Studies based on patient outcomes |
| 3a | Systematic review of case–control studies |
| 3b | Single case–control study |
| **C** | 4 | Case series reports, low-quality cohort studies and low-quality case–control studies |
| **D** | 5 | Expert opinion (i.e., speculation based solely on basic research or clinical experience that is not supported by clinical studies) |

**Table 2: Liver function indicators of patients with HCC using ICIs.**

|  | **Suggested scope** |
| --- | --- |
| ***Blood biochemistry*** |  |
| Alb | ≥30 g/L |
| ALT | <5 × ULN |
| AST | <5 × ULN |
| TBil | <5 × ULN |
| Creatinine ≤1.5 × ULN or creatinine clearance rate ≥50 mL/min (calculated using Cockrofer Gault formula) | |
| ***Coagulation function*** |  |
| INR | ≤2 × ULN |
| Urine protein | <++ or 24-h urine protein quantification <1.0 g |

Alb: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HCC: Hepatocellular carcinoma; ICIs: Immune checkpoint inhibitors; INR: International Normalized Ratio; TBil: Total bilirubin.

**Table 3: Half-life of common ICIs.**

| **ICIs** | **Target** | **Half-life (days)** |
| --- | --- | --- |
| Nivolumab | PD-1 | 25.0 |
| Pembrolizumab | PD-1 | 22.0 |
| Camrelizumab | PD-1 | 5.5 |
| Toripalimab | PD-1 | 12.6 |
| Sintilimab | PD-1 | 19.6 |
| Tislelizumab | PD-1 | 13.3 |
| Penpulimab | PD-1 | 23.3 |
| Cemiplimab | PD-1 | 19.0 |
| Atezolizumab | PD-L1 | 27.0 |
| Durvalumab | PD-L1 | 18.0 |
| Avelumab | PD-L1 | 6.1 |
| Ipilimumab | CTLA-4 | 14.7 |

ICIs: Immune checkpoint inhibitors.