Jordan Medical Journal

REVIEW ARTICLE

Evaluating Standardization of Neoadjuvant Immunotherapy in Transplant-Eligible Hepatocellular Carcinoma Populations

Abdullah Esmail[1], Yaser Rayyan[2], Hashim Rayyan[2] and Maen Abdelrahim[1*]

[1] Section of GI Oncology, Houston Methodist Cancer Center, Houston Methodist Hospital, Houston, TX, United States.

[2] Department of Gastroenterology & Hepatology, Faculty of Medicine, The University of Jordan, Amman, Jordan

*Corresponding author:

mabdelrahim@houstonmethodist.org

Received: January 30, 2025

Accepted: February 2, 2025

DOI:
https://doi.org/10.35516/jmj.v59i1.3957

Abstract

In the past decade, immunotherapy has significantly revolutionized the treatment of advanced hepatocellular carcinoma (HCC). Recent phase III trials examining immunotherapy as monotherapy and combination therapy for early to intermediate-stage HCC have produced favorable results, while further phase III trials in this patient cohort are ongoing. Owing to the advantageous data derived from these trials, the utilization of immunotherapy is broadening to include patients with earlier stages of HCC, especially within the transplant-eligible subgroup. Current literature increasingly advocates for the standardized application of neoadjuvant immunotherapy in liver transplantation. Transplantation functions as a potentially curative treatment for HCC and additionally restores normal, healthy liver function. Immunotherapy in pre-transplant patients may improve downstaging efficacy and tumor management, though it carries immunological risks. Immune-related toxicities are substantial in individuals with chronic liver disease, who are particularly susceptible, alongside the risk of acute rejection post-transplantation. The main goal of immunotherapy in this population is to improve access to liver transplantation while preserving pre- and post-transplant results. This concise review analyzes contemporary literature regarding the use of immunotherapy in the neoadjuvant context prior to liver transplantation, explores potential advantages of combination immunotherapy, and synthesizes important recent clinical findings from prominent trials related to HCC transplant oncology treatment.

Keywords: Hepatocellular carcinoma, liver transplant, Immune checkpoint inhibitors, Transplant oncology.

INTRODUCTION

Immunotherapy has profoundly transformed cancer treatment, particularly for hepatocellular carcinoma (HCC), which is the third foremost cause of cancer-related mortality globally [1-3]. Shifting dynamics in transplants oncology care can primarily be attributed to an increase in social awareness to the field itself. While relatively primitive to believe, the coined field of medicine has only been official since 2015 and

has had exponential growth in all terms of care; be that surgical technique, drugs and their respective combinations with localized treatments, new surveillance measures, and increased reliance on biomarker analysis data. Though the true measure of growth in this field can best be determined by improved survival outcomes for the patients that undergo treatment, further demonstrated by the multiple FDA approved immunotherapy regimens in the past decade [4]. Immune check point inhibitors (ICPIs) are antibodies that block essential regulatory signals that dampen the immune response, enabling tumor-reactive T cells to successfully participate in an anti-cancer response, even in the immunosuppressive environment of the tumor microenvironment. These proteins participate in the downregulation of the host's response to tumors, while ICPI therapy subsequently inhibits tumor cells from evading T cell-mediated immune defenses [5, 6]. ICPI primarily enhances the innate immune response to identify foreign threats and stimulates anti-tumor activity, while offering relatively restricted toxicities compared to conventional chemotherapy interventions. Although the complete mechanism of ICPIs is not fully understood, several proposed mechanisms have been suggested. The decrease and loss of regulatory T cells (Treg cells) are essential elements, as these immune cells are crucial for maintaining the resistance produced by ICPI treatment, particularly in relation to CTLA-4 blockade. The decrease in Treg cells leads to a reduction in anti-inflammatory cytokines, subsequently promoting the proliferation of CD8+ T cells [7]. Moreover, early changes in B cells, such as the rise of the CD21lo subtype, may lead to the activation of autoreactive B cells, which can cause immune-related adverse events (irAEs) [7]. The significant effectiveness of ICPIs requires a comprehensive assessment of the treatment risks in comparison to their therapeutic benefits. Adverse events associated with the immunologic mechanism of action in immunotherapy are commonly referred to as irAEs. They appear in a way that differs from the adverse events associated with traditional chemotherapy, exhibit a less predictable timeline, and often last for a longer period. Various ICPI-containing regimens are presently recognized as efficacious first-line treatments for advanced HCC, demonstrating enhanced overall survival (OS) relative to sorafenib, the formerly established first-line systemic therapy for HCC [8-13]. There is significant literary interest in utilizing immunotherapy for transplant-eligible HCC, due to its efficacy as a "downstaging" method to enhance eligibility for curative surgical interventions. This review examines the existing rationale and literature data, showcasing emerging evidence of effective ICPI application in neoadjuvant liver transplant (LT) cohorts. In addition to assessing significant risks and immunological toxicities associated with ICPI administration in the primary liver cancer cohort, for whom LT may offer a conclusive remedy for both the underlying liver condition and HCC [2, 3, 9-18]. The presentation of neoadjuvant immune checkpoint inhibitor treatments is advancing transplant oncology, resulting in a significantly larger pool of transplant eligible patients in the future.

Expansion of LT: transplant eligibility

There are limited curative treatment options for patients with primary liver cancers, 90% of which are identified as HCC. LT has emerged as a feasible therapeutic alternative for patients who exceed the criteria for initial resection, which is the primary curative approach for HCC treatment. The Milan criteria have served as the "gold standard" for transplant eligibility for over 25 years, following a study by

Mazzaferro et al. [19], and represent a specific guideline for the management of HCC. The criteria stipulate that for qualification, disease burdens must consist of either a single tumor measuring less than 5 cm or up to three tumors each measuring less than 3 cm, in addition to the absence of macrovascular invasion or extrahepatic metastasis. Despite the rigorous qualification criteria, the sustained success of the boundaries has permitted ongoing utilization, even in the present day. Eligibility for LT has been significantly broadened in various trial studies over the past 25 years (Table 1), and different institutions and countries may employ distinct eligibility criteria. Proposed expanded criteria, encompassing the University of California, San Francisco (UCSF) criteria [20], the up-to-seven criteria [21], total tumor volume, the alpha-fetoprotein (AFP)-French criteria [22], the Canadian expansion of Toronto criteria [23], and Metroticket 2.0 [24], suggest that enhancing access to liver transplantation for patients surpassing the Milan criteria is achievable while maintaining favorable post-transplant outcomes [25].

Table 1. Visual expansion of Milan criteria following its initial successful utilization.

References	Year Updated	Description	5-year OS	5-year DFS
Milan Criteria [19]	1997	1 lesion ≥2 cm and ≤5 cm **OR** up to 3 lesions, each ≥1 cm and ≤3 cm There must be no evidence of vascular invasion or extra-hepatic disease	75% (4-yr)	83% (4-yr)
UCSF Criteria [20]	2001	Solitary ≤6.5 cm, **OR** ≤3 nodules ≤4.5 cm TTD ≤8 cm	75%	81%
Dallas Criteria [26]	2007	Solitary ≤6 cm **OR** 2-4 nodules ≤5 cm	61.8%	80%
Valencia Criteria [27]	2008	≤3 nodules ≤5 cm TTD ≤10 cm	69%	NA
UP-to-7 Criteria [21]	2009	Total size and the number of tumors not exceeding 7, in the absence of microvascular invasion	71.2%	NA
Kyoto Criteria [28]	2010	Number of lesions ≤10 Maximal diametr of each tumor ≤5 cm PIVKA-II ≤400mAU/ML	82%	NA
French Criteria, [22]	2012	0/1/4 Points for tumor size (≤3 / ≤6 / >6 cm) 0/2 points for number (≤3 / ≥4) 0/2/3 points for AFP (≤100 / ≤1,000 / >1,000 ng/ml) respectively, (with a total added points of ≤2 considered low risk for recurrence)	68%	NA
Edmonton Criteria [29]	2015	TTV ≤115 cm^3 AFP ≤400 ng/ml	74.6% (4-yr)	NA
Toronto Criteria [23]	2016	Milan criteria: Any size and number + GI-2 + no cancer-related symptoms AFP ≤500 ng/ml	78%	NA
Metroticket 2.0 [24]	2018	(number+size) Up-to-7: AFP ≤200 ng/ml Up-to-5: AFP ≤400 ng/ml Up-to-4: AFP ≤1000 ng/ml	70%	NA

AFP: alpha-fetoprotein, TTD: total tumor diameter; TTV: total tumor volume; NA: not available, DFS: disease free survival; PIVKA-II: protein induced by vitamin k absence-II.

The expanding eligibility for LT may benefit patients and physicians seeking broader access to curative treatment for HCC; however, organ availability poses a significant barrier to therapeutic advancement. While it is advantageous for medical professionals to offer the highest proportion of patient's curative treatment options, the limited availability of donor organs is effectively extending the neoadjuvant period for ICPI intervention. Patients who initially exceed Milan or other criteria may qualify for liver transplantation after successful downstaging. Successful downstaging reduces tumor size and is associated with well-differentiated HCC histology and the absence of microvascular invasion, indicating improved tumor biology [30]. In Europe, no established criteria exist for downstaging. Patients with tumors that have ceased growth in other organs or large blood vessels may qualify for a liver transplant. Locoregional therapies (LRTs) serve as the principal approach for downstaging at present [31]. These therapies exert three significant effects on immunotherapy: they enhance downstaging success, thereby increasing accessibility to liver transplantation for patients who initially do not meet selection criteria due to tumor size; they maintain disease control for patients on the waiting list, reducing dropout rates; and they expand downstaging options by addressing potential hidden extrahepatic micrometastasis through systemic therapy [32, 33].

Tumor downstaging in HCC populations

The outcomes regarding the advantages of LT for individuals with HCC and an excessive disease burden are inconclusive. This is a general statement that requires segmentation to follow the descriptions of disease burden in the context of HCC and the criteria classified as "normal" for HCC liver transplantation. This primarily arises from the challenge of forecasting significant biological issues prior to transplantation. Factors influencing this include microvascular invasion, microsatellites, tumor grading, cellular mutations, and the capacity of the liver parenchyma and tumor microenvironment to independently induce cancer [20]. Complications of primary liver disease that may arise during treatment, complicating the attainment of curative outcomes.

This underscores the heightened literary emphasis on liquid and tumor biopsies in patients with HCC [34, 35]. Liquid biopsies have experienced a significant increase in standard use due to current literature highlighting the advantages of this non-invasive surveillance method. A blood test evaluating various biomarkers, AFP levels, and, in instances of recurrent monitoring, minimal residual disease (MRD). The primary advantage of MRD is its ability to detect circulating residual tumor DNA before any subsequent tumor becomes sufficiently large to be identified through standard imaging techniques [36-38]. In the absence of validated molecular biomarkers for precise predictions of HCC recurrence risk, the tumor's response to appropriate treatments serves as the most reliable indicator of tumor biology in clinical decision-making.

In addition to the Milan criteria, extended criteria may be utilized for transplant candidates with HCC, permitting patients to receive treatment until the tumor burden meets the Milan criteria. 'Downstaging' denotes the application of locoregional therapy (LRT) to reduce tumor burden to thresholds that meet the requirements for orthotopic liver transplantation (OLT), typically the Milan criteria [39].

Downstaging is a particular result of effective neoadjuvant anti-cancer therapy employed in transplant oncology, which has become particular useful in maintaining and improving PFS and OS of patients on LT waitlist through ICPI utilization Figure 1.

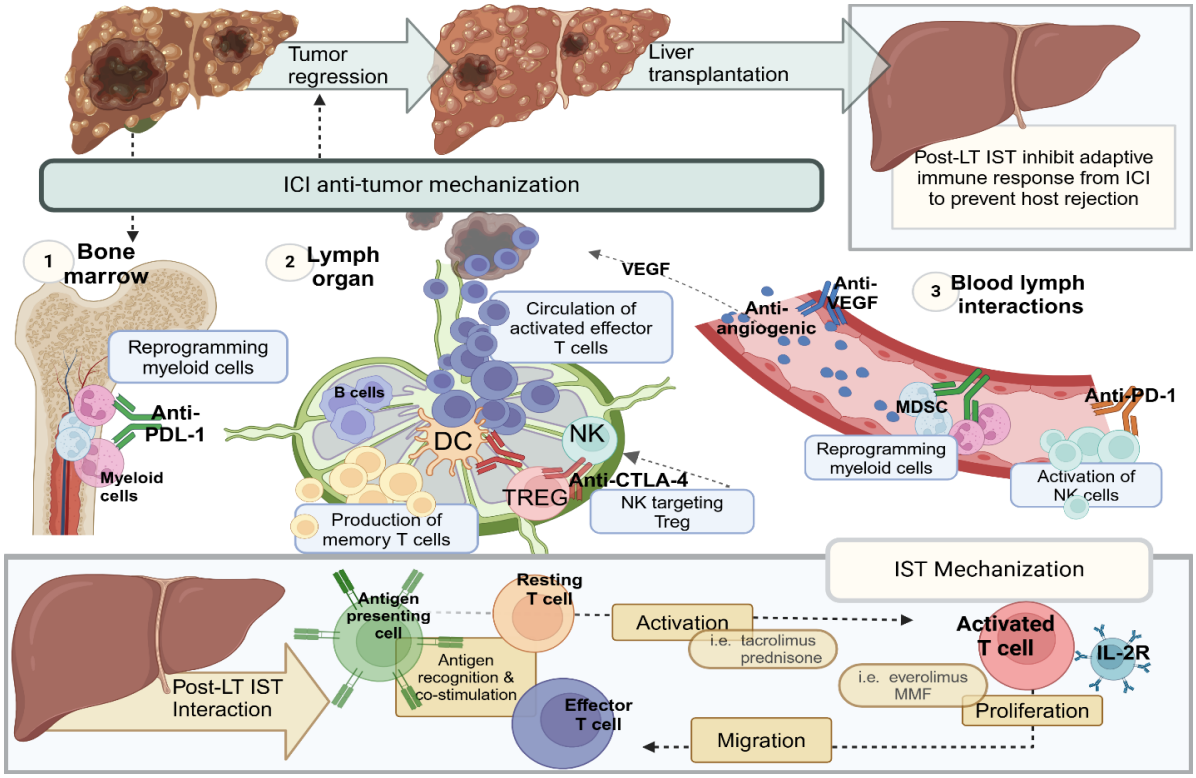

Figure 1. Anti-tumor adaptive immune response mediated by variant ICI in 1) bone marrow, 1) lymph nodes, 3) blood vessels, and the eventual affected liver microenvironment. Segmented below, basic mechanics to the immune mediated response to immunosuppressive intervention following transplantation. ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte antigen-4; DC, dendritic cell; MDSCs, myeloid-derived suppressor cells; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; IST, immunosuppressive therapy; LT, liver transplant; i.e., in example.

This method facilitates the assessment of tumor biology through the observation of tumor dynamics over time. Histological markers indicative of a favorable prognosis in treated HCC are often correlated with a positive response to downstaging. The markers consist of the lack of microvascular invasion, low tumor grade, and the absence of satellite lesions, analogous to the Milan criteria that patients must fulfill at the time of transplantation [40]. Data from trials and extensive cohort studies demonstrate that liver transplantation, following successful and sustained downstaging, provides advantages over non-transplant care, particularly regarding overall and tumor-free survival rates. [41-43]. The data suggests that patients with tumor burdens exceeding standard criteria necessitate downstaging as a crucial prerequisite for liver transplantation,

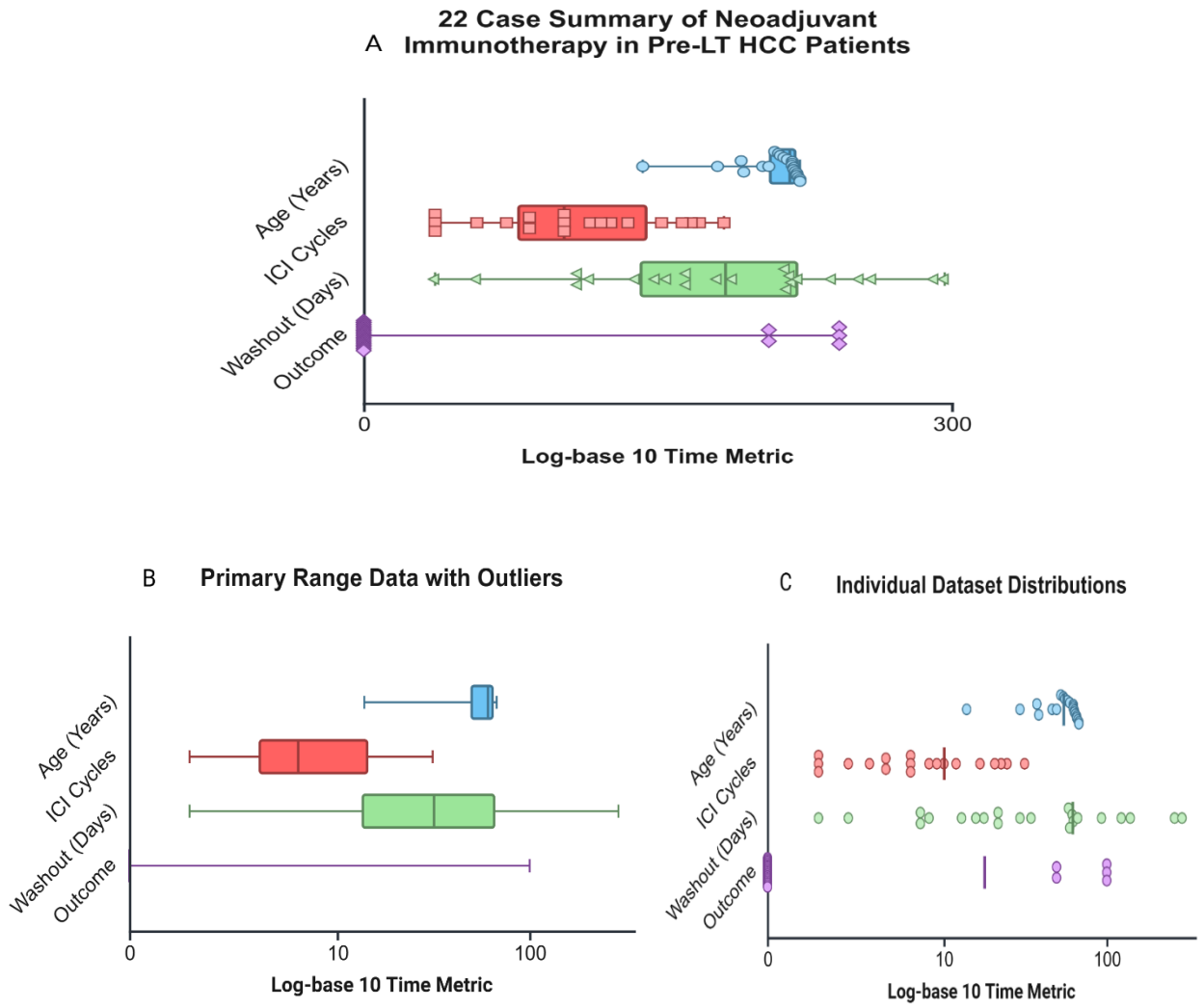

Figure 2. Clinical data from the patient pre-LT HCC cohort by a scale of log-base 10. Graph A is a conglomeration of range data, with a linear median line, individual plotted data points, and outlier range scales. Graph B is descriptive of a standard boxplot graph, with linear data that only has a single dependent variable. The boxed graphing demonstrated standard deviation of the datasets from several case studies ([44-52]), horizontal demonstration of outliers, and a vertical median point. Graph C represents the individual data variables. *Outcome data has been numerically coded for graphing representation, 0, no rejection; 50, rejection resolved; 100, rejection.

must also undergo continuous locoregional therapy until an optimal response is attained prior totransplantation. For patients who surpass conventional criteria, existing societal guidelines recognize the response to neoadjuvant therapies as a pivotal determinant in transplant allocation [53, 54]. Figure 2.

Advocates for more stringent upper limits on downstaging, akin to the UNOS-downstaging criteria, are linked to a heightened risk of patients opting out of the waiting list and facing microvascular invasion in liver transplants [30, 55]. AFP levels that surpass 100 ng/ml and drop below 20 ng/ml after downstaging treatments serve as important markers in risk stratification. The former is linked to a higher chance of

waitlist dropout because of tumor progression, whereas the latter is associated with a recurrence probability of under 10% following liver transplantation. A multicenter US cohort has determined that the absolute AFP response after LRT serves as the most dependable indicator of tumor biology [55, 56]. Additionally, the dynamics of AFP after treatment and the morphometric parameters of tumors could help in identifying patients who are at risk for failure in downstaging [24, 57-59]. In the United States, patients with an AFP level greater than 1,000 ng/ml cannot receive standard MELD exception points unless their AFP level is lowered to below 500 ng/ml via treatment [60, 61].

All progress in HCC downstaging took place prior to the beginning of the current immunotherapy era. Current prospective studies suggest that downstaging strategies improve access to liver transplantation for hepatocellular carcinoma, supported by the proven effectiveness of different immunotherapy methods, whether used alone or in conjunction with locoregional therapy (LRT). In this context, two additional factors accompany the recognized benefits of downstaging. The biological processes that result in diminished effectiveness suggest that simply lowering tumor burden, as shown by cross-sectional imaging, is not enough [62, 63]. Systemic immune-driven strategies can more effectively achieve optimal downstaging by increasing the chances of targeting occult micrometastasis, broadening tumor-free margins, and generating a response that reduces the risk of recurrence. The idea of utilizing HCC tissue after immunotherapy needs to be reevaluated to include factors related to the patient's immune system and the tumor microenvironment [64]. This is similar to the use of tumor burden scores in predicting outcomes after resection [65, 66].

Clinical downstaging with ICI prior to LT

Although LT is contraindicated in patients with advanced HCC, certain individuals have been shown to achieve a robust and sustained complete response, following immunotherapy intervention. Case reports have documented successful LT in patients who exhibit exceptionally durable responses to ICI treatment [50, 67]. The rising prevalence of HCC, alongside the widespread implementation of immunotherapy as the standard treatment for advanced HCC, suggests that an increasing number of patients receiving ICIs may unexpectedly qualify for LT.

The efficacy of immunotherapy in downstaging is robustly supported by data from EMERALD-1. Although EMERALD-1 was not specifically designed to address questions regarding LT, the patient population, primarily consisting of individuals with intermediate-stage HCC, and the non-ICI therapy utilized (TACE) reflect the pre-LT population that undergoes LRT for either downstaging or to mitigate the risk of waitlist dropout. Consequently, we can infer that immunotherapy enhances the efficacy of HCC treatment in the pre-LT population. Furthermore, emerging data indicate that pathological response, defined as the extent of non-viable tumor resulting from immune checkpoint inhibitor treatment in resection specimens, correlates with recurrence-free survival. This finding aligns with data from liver resection therapy studies, which suggest that adopting a more aggressive treatment objective aimed at eliminating viable disease is more effective than merely adhering to Milan criteria. EMERALD-1 and other ongoing phase III clinical trials do not elucidate the safety of neoadjuvant immunotherapy prior to liver

transplantation, especially concerning the risk of allograft rejection following the procedure.

Multiple case reports and series indicate that pre-liver transplantation immunotherapy is typically safe. Tabrizian et al. reported on nine patients who underwent liver transplantation following treatment with nivolumab monotherapy, noting only one instance of mild acute rejection [45]. Wang et al. conducted the largest published series to date, involving 16 patients treated with various anti-PD-1 monotherapies. Acute rejection was observed in nine patients; however, rejection was defined by elevations in liver tests rather than histological analysis, and importantly, there were no instances of graft loss [68]. In the literature, more than 60 patients undergoing immunotherapy prior to LT have been documented, with three instances of graft loss, all occurring in patients who received ICI therapy within 90 days of LT [69]. Tabrizian et al. presented results from a multicenter study involving 80 patients with HCC treated with ICIs, of whom 30 had undergone LT by the time of abstract publication. Rejection was observed in five patients (16.7%), with a single instance of graft loss (3.3%). Consistent with previous studies, the two severe rejection cases, including the graft loss, were in patients who underwent ICI treatment within 90 days post-LT [70]. A 90-day washout period, informed by existing evidence and the half-life of ICIs (18-27 days), may be a reasonable approach to mitigate the risk of severe post-LT rejection. However, considering that the effects of ICIs can extend beyond their pharmacokinetic half-life—due to long-term durable treatment responses and the potential for irAEs to manifest 6-12 months post-therapy cessation—a washout period does not ensure complete safety. Most patients reported in the literature underwent anti-PD-1 monotherapy, whereas one of the two standard care immunotherapy regimens (STRIDE) involves an anti-CTLA-4/PD-L1 combination therapy, potentially leading to a higher risk of immunologic complications. Considering that all ICI trials exclude patients with autoimmune diseases, we advise caution regarding the use of neoadjuvant immunotherapy prior to liver transplantation in patients with autoimmune hepatitis due to their presumed heightened risk of disease flare and post-transplant rejection.

Multiple current studies are evaluating the safety and efficacy of neoadjuvant immunotherapy in patients awaiting liver transplantation. ESR-20-21010 is a single-arm, phase II trial assessing the STRIDE regimen in patients awaiting liver transplantation with tumor burden meeting UCSF criteria, with the primary endpoint being post-transplant rejection. Participants in ESR-20-21010 will undergo STRIDE treatment for a duration of up to 4 months, following a minimum washout period of 72 days prior to LT. The PLENTY trial is a single-center study examining the combination of pembrolizumab and lenvatinib, a tyrosine kinase inhibitor, in patients awaiting liver transplantation with tumor burden surpassing the Milan criteria. The primary endpoint is recurrence-free survival, while adverse events, including rejection, serve as a secondary endpoint. Participants are required to have a minimum pembrolizumab washout period of 42 days. The ImmunoXXL study (NCT05879328) is an observational prospective single-arm multicenter study conducted in Europe. It aims to investigate the efficacy of liver transplantation in hepatocellular carcinoma patients who exhibit a partial or complete and

sustained response (greater than three months) to atezolizumab and bevacizumab, specifically targeting a post-transplant survival rate of 60% or higher as determined by the Metroticket 2.0 calculator. Patients exhibiting extrahepatic spread or macrovascular invasion are excluded from consideration. A minimum washout period of 30 days before liver transplantation is necessary.

Immunotherapy in HCC and combinate LRT utilization

ICPI-based regimens are now utilized as the primary treatment for patients with advanced HCC, and their efficacy is suggestive of potential application in earlier-stage disease. Previous research has primarily focused on evaluating the effectiveness of ICPI monotherapy; however, current standard of care now predominantly includes combination therapy [71, 72]. Two significant trials, IMbrave150 and HIMALAYA, demonstrated considerable improvements in overall and progression-free survival (PFS) for patients with unresectable HCC receiving ICPIs compared to those treated with sorafenib, a multikinase inhibitor that had been the sole approved systemic therapy for HCC for nearly a decade [73-75]. The IMbrave150 trial [73] investigated the efficacy of pairing atezolizumab, an anti-PD-L1 agent, with the anti-angiogenic medication bevacizumab, ultimately demonstrating that the combination of atezolizumab and bevacizumab surpassed sorafenib, resulting in a median overall survival of 19.2 months compared to 13.4 months, along with objective response rates (ORR) of 30% versus 11% [76]. The HIMALAYA trial explored a novel combination therapy that employs two distinct immune checkpoint inhibitors: durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4). Data from a phase II trial indicated that durvalumab and tremelimumab were combined in the STRIDE regimen, which consists of a single priming dose of tremelimumab followed by monthly durvalumab infusions. STRIDE demonstrated improved overall survival compared to sorafenib, with a median of 16.4 months versus 13.8 months, and was linked to a significantly higher objective response rate of 20.1% in contrast to 5.1% [74].

The CARES-310 study (NCT03764293), [77] represents the third phase III trial of a regimen incorporating an immune checkpoint inhibitor, showcasing favorable results. Patients in the CARES-310 investigational arm were treated with camrelizumab (anti-PD-1) in combination with rivoceranib, an oral tyrosine kinase inhibitor that specifically targets VEGFR-2. Camrelizumab and rivoceranib therapy demonstrated enhanced overall survival, with a median of 22.1 months in contrast to 15.2 months, alongside a greater overall response rate (ORR) of 25% compared to 6% for sorafenib therapy [77]. Camrelizumab and rivoceranib have undergone recent FDA NDA resubmission for utilization as a frontline treatment in unresectable HCC patients, citing the CARES-310 data. Current guidelines suggest that atezolizumab combined with bevacizumab or STRIDE are the recommended first-line regimens for untreated advanced HCC. At present, there are no available studies that directly compare ICPI regimens against one another. Comprehensive analysis of significant HCC cohort immunotherapy trials has indicated that first-line combination regimens showed similar hazard ratios for OS in comparison to initial standard of care, sorafenib [78, 79]. Though the relationship between the causes of liver disease and the efficacy of

immunotherapy remains ambiguous. Initial findings from both preclinical and clinical studies indicate that treatment with immune checkpoint inhibitors may show diminished effectiveness in patients suffering from metabolic dysfunction-associated liver disease. Data from major ICPI trials have not clearly shown any differences in treatment response depending on the type of liver disease [80, 81].

TACE, TARE, and ablation serve as an essential locoregional treatment option for early to intermediate-stage hepatocellular carcinoma, particularly for downstaging or minimizing the risk of waitlist dropout in patients who are awaiting liver transplantation. The treatments promote the release of tumor antigens and pro-inflammatory cytokines, resulting in a "priming" effect on adaptive immunity through the activation of T cells by antigen-presenting cells [82, 83]. Patients that demonstrate T-cell response after TACE or TARE experience enhanced clinical outcomes. Immunotherapy could show a combined effect within the immunogenic microenvironment established by TACE or TARE. This has generated significant interest in exploring the efficacy of combining immunotherapy with LRT in intermediate-stage HCC [84, 85]. Several international phase III trials are presently enrolling participants to investigate different regimens that include immune checkpoint inhibitors alongside transarterial chemoembolization, with progression-free survival compared to transarterial chemoembolization alone as the main outcome measure. The combination of LRT and immunotherapy is generally well-accepted, and it is expected that immunotherapy will be integrated for patients who would have previously received LRT alone [86, 87].

Risks for immunotherapy utilization

Although the precise mechanisms behind irAEs are not fully understood, they are thought to stem from the bystander effects of activated T-cells, which correspond with the action mechanisms of ICPIs [88, 89]. Tumors that exhibit inflammation with cytotoxic T lymphocytes prior to treatment experience further inflammation and tumor cell death following the administration of immune checkpoint inhibitors. Similarly, an organ showing subclinical inflammation may experience considerable, clinically noticeable inflammation following the removal of essential negative regulators of T-cell function. However, the processes that lead to specific toxicities in certain patients, along with the connection between toxicity and therapeutic response, are still not well understood.

Preliminary research has begun to explore these molecular mechanisms. Studies suggest that irAEs could be triggered by antigens that are common to both tumors and inflamed organs. This model suggests that activated T cells interact with both tissues, leading to a combination of toxicity and an immune response. A post-mortem study of two metastatic melanoma patients who developed fulminant myocarditis after treatment with nivolumab plus ipilimumab showed the presence of infiltrating T-cells and macrophages in the myocardial tissue and cardiac conduction system [90]. An extensive examination of infiltrating T-cells through T-cell receptor (TCR) sequencing revealed common high-frequency TCRs present in cardiac muscle, skeletal muscle, and tumor tissue. A recent prospective cohort study involving 73 NSCLC patients treated with anti-PD-1 antibodies revealed that 34.2% of patients experienced dermatologic irAEs

[91]. TCR clonotype analysis was performed on samples from four patients with matched skin and tumor biopsies, revealing that shared T-cell clones between skin and tumor were found in all patients. Following experiments revealed nine candidate shared antigens between skin and tumor that successfully triggered interferon gamma-based T-cell responses in stimulated peripheral blood mononuclear cells from patients experiencing dermatologic irAEs.

Further research underscores the connection between T-cells and irAEs, highlighting the significance of the gut microbiome. Significant differences in microbial diversity and composition have been noted between melanoma patients who respond to anti-PD-1 therapy and those who do not; several studies suggest that specific species may be more prevalent in responding patients compared to non-responders [92, 93]. Research utilizing fecal microbiome transplants in mouse models across multiple studies has yielded valuable mechanistic insights. Mice that received stool transplants from patients responding to anti-PD-1 antibodies showed a higher density of CD8 T-cells in the tumor tissue. Mice that received stool transplants from patients who responded showed higher concentrations of CD8 T-cells in the gut than those that received stool from non-responders. A study involving 26 metastatic melanoma patients treated with ipilimumab revealed that those with baseline gut microbiota enriched in faecalibacterium and other firmicutes members showed better PFS, OS, and higher rates of ICPI-induced colitis compared to patients without such enrichment [94]. Patients with a higher presence of firmicutes showed a lower percentage of regulatory T-cells and alpha 4 beta 7 integrin positive CD4 and CD8 T-cells in comparison to those without this enrichment. The composition of the microbiome may be linked to both toxicities and responses; however, the importance of different microbial species remains unclear. Further prospective studies are necessary.

Further research suggests that there are autoimmune toxicity mechanisms that function independently of the anti-tumor response. In a hypophysitis model linked to ipilimumab, SJL mice were treated with an IgG1 hamster antibody that inhibits CTLA-4, given at a dosing schedule comparable to that utilized in humans [95]. Mice treated with the anti-CTLA-4 antibody displayed a distinct lymphocytic infiltrate in the pituitary gland. No infiltration was noted in other organs of the treated mice, such as the thyroid gland, skin, colon, or liver. No pituitary antibodies were found in either the pre-treatment mice or the control groups. CTLA-4 mRNA expression was detected in the murine pituitary gland, mainly in lactotrophic and thyrotrophic cells, while significantly lower levels were noted in the murine thyroid gland. This study suggests that the expression of organ-specific antigens that are already present may play a role in autoimmune toxicity resulting from immune checkpoint inhibitors, regardless of any common effects related to anti-tumor activity.

Pre-transplant population in ICPI utilization in HCC LT cohorts

ICPIs function by modifying the regulatory mechanisms of the immune system, leading to a significant occurrence of irAEs that resemble autoimmune disorders and can impact almost all organ systems. Severe irAEs are immune toxicities that necessitate systemic corticosteroid or immunomodulatory treatment and typically result in the cessation of ICPI therapy.

Patients diagnosed with HCC encounter high-grade irAEs at rates comparable to those seen in other types of cancer, ranging from 10% to 20%, contingent upon the particular ICPI regimen employed [73, 74, 96, 97]. Individuals diagnosed with HCC represent a susceptible population concerning irAEs as a result of pre-existing liver conditions. Considering that up to 90% of patients with HCC have underlying cirrhosis [98], there are concerns about the possibility of irAEs causing hepatic decompensation. Hepatic decompensation refers to significant functional deterioration of the liver, frequently associated with complications arising from liver cirrhosis. This condition can be initiated by significant inflammation in other organs or by direct inflammation of the liver, like ICPI hepatitis, leading to a decline in liver function and portal hypertension. ICPI hepatitis is a frequent and serious immune-related adverse event, affecting 2-10% of patients, depending on the treatment regimen. Furthermore, ICPI hepatitis is the immune-related adverse event that is most likely to manifest as high-grade at the time of occurrence [99-101]. Determining the root cause of increased liver tests in individuals with cirrhosis and liver cancer presents considerable difficulties. A study with 375 patients receiving atezolizumab and bevacizumab indicated that the incidence of immune checkpoint inhibitor hepatitis was 11.4%. Furthermore, 6-9% of patients in phase III clinical trials required corticosteroid therapy for immune checkpoint inhibitor hepatitis [73, 74, 77]. Clinical trial data indicate the potential for hepatic decompensation, with reported occurrences of ascites (6-7%), portal hypertension-related bleeding (1-4%), and encephalopathy (1-3%). Although these trials did not explore the suspected causation, particularly the timing between an irAE and a decompensating event, and some reported decompensating events likely stemmed from the natural progression of liver disease, the fact that only patients with excellent baseline liver function (Child-Pugh class A) were included in all three trials indicates that the development of irAE may lead to hepatic decompensation in a specific subset of patients [102]. Furthermore, it suggests that decompensation might happen more often in real-world scenarios involving immunotherapy for individuals with advanced liver disease [103]. Findings from a small clinical trial and a meta-analysis suggest that treating patients with Child-Pugh class B disease is achievable, demonstrating similar rates of irAEs as those seen in patients with Child-Pugh A cirrhosis [104, 105]. However, the lack of decompensation data and the observation that patients with Child-Pugh B cirrhosis show decreased overall survival indicate that further research is needed [104, 106].

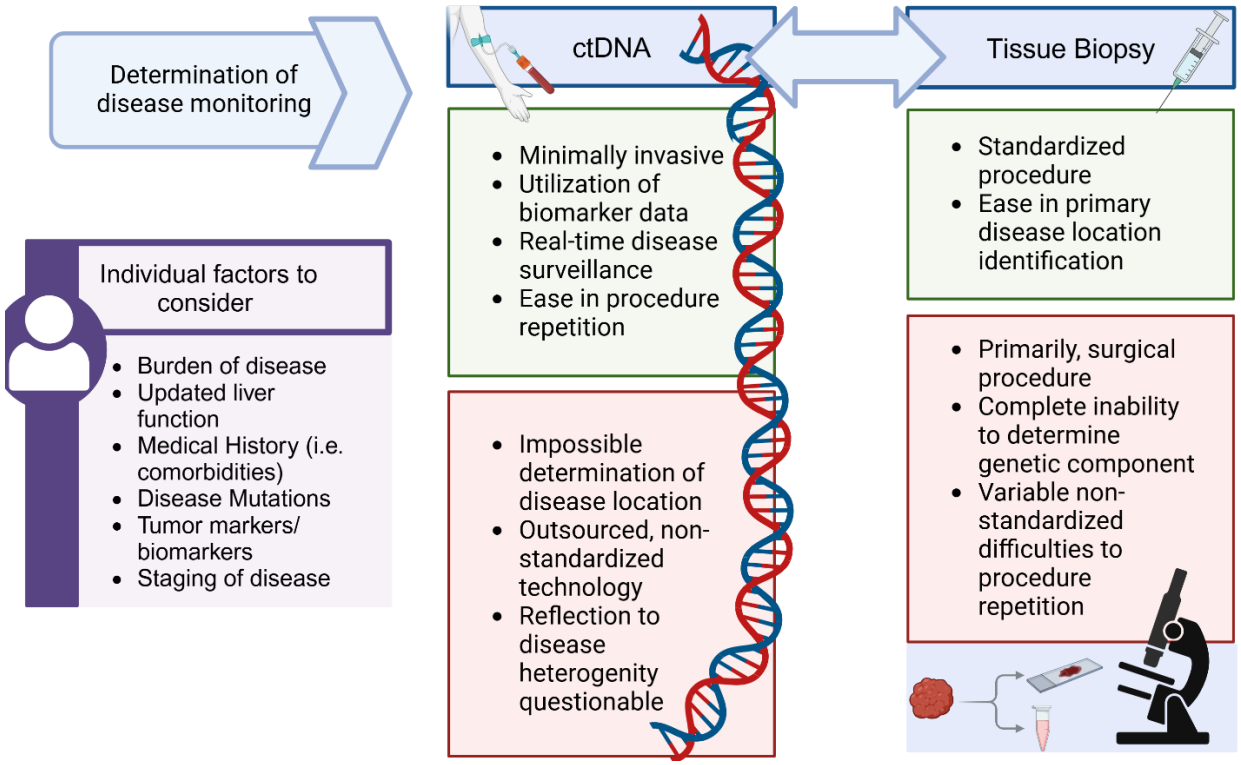

Figure 3. Risk analytics in HCC staging, weighing the risks and benefits of surveillance and staging techniques to determine treatment that will bring best outcomes. ctDNA, circulating tissue DNA; HCC, hepatocellular carcinoma; ICPI, immune checkpoint inhibitor; LRT, locoregional therapy; LT, liver transplantation; PFS, progression-free survival; ORR, objective response rate.

Combination therapy demonstrates greater effectiveness in treating HCC compared to ICPI monotherapy, which adds additional complexity concerning toxicity considerations. Combination therapy using anti-CTLA-4 and PD-(L)1 is associated with a higher occurrence of irAEs compared to ICPI monotherapy, as shown in multiple cancer studies. The increased risk is associated with enhanced immune activation resulting from dual checkpoint blockades. This phenomenon is also observed in HCC, where 12% of patients in IMbrave150 [73] received corticosteroid therapy for presumed irAEs , in contrast to 20% of patients in HIMALAYA [74]. Conversely, non-ICPI agents such as bevacizumab are associated with toxicities. Bevacizumab significantly elevates the risk of gastrointestinal bleeding [107, 108] (Table 3). Patients with HCC who qualify for bevacizumab-containing regimens need to be screened for varices and must undergo suitable treatment before starting the bevacizumab component. Bevacizumab may lead to proteinuria and renal toxicity, presenting a considerable risk of acute kidney injury for patients with cirrhosis. Bevacizumab negatively affects wound healing; therefore, a washout period of at least 60 days is advised for patients eligible for liver transplantation, as noted in surgical literature [109].

TABLE 3. CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; LT, liver transplantation. ∗ Includes atezolizumab (in combination with bevacizumab, IMbrave150) and durvalumab (monotherapy arm from HIMALAYA), camrelizumab (in combination with rivoceranib, CARES-310). # For post-LT outcomes, data aggregated from currently available case reports and case series. Nivolumab was the most common ICPI reported, but another anti-PD-(L)1 monotherapy included pembrolizumab, durvalumab, atezolizumab, sintilimab, and camrelizumab. ^ Includes durvalumab/tremelimumab (combination arm from HIMALAYA).

Toxicity or adverse outcome	Anti-PD-(L)1∗, #	Combined anti-PD-(L)1/CTLA-4^	VEGR
Any immune-mediated toxicity requiring immunomodulatory therapy	10–16%	19.5%	–
Ascites	6.5%	6%	–
Colitis requiring steroid treatment	1.5%	5%	–
Encephalopathy	1.5%	2%	–
Gastrointestinal perforation	–	–	1%
Hepatitis requiring steroid treatment	6.5%	8.5%	–
Nephritis and/or acute kidney injury	–	–	1–5%
Proteinuria	–	–	20–44%
Portal hypertension-related bleeding	1%	1%	~3%
Post-LT rejection	17–33%	–	–
Wound healing complications	–	–	1%
Post-LT death from graft loss or hepatic necrosis	5%	–	–

In contrast to the advanced HCC population, which demonstrates greater tolerance for toxicities due to the significant benefits of immunotherapy compared to other systemic treatments, the modest advantages of adjuvant immunotherapy or combined immunotherapy/LRT in the pre-LT population may necessitate a more selective strategy. The IMbrave050 trial, in conjunction with the adjuvant sintilimab trial and other ongoing phase II-III adjuvant studies, has restricted enrollment to patients identified as high risk for recurrence. This encompasses individuals anticipated to gain the greatest advantage, along with those classified as Child-Pugh class A liver disease, who possess the highest hepatic reserve and are best equipped to endure toxicities. Trials incorporating combined immunotherapy and TACE expand patient eligibility to include individuals with Child-Pugh class B7 liver disease. This adjustment acknowledges the typically more compromised patient population eligible for TACE, while ensuring adequate preservation of liver function [110]. The lack of biomarkers indicating treatment response or the onset of immune-related adverse events in patients with hepatocellular carcinoma undergoing immunotherapy represents a significant clinical gap [88]. Future research targeting this knowledge gap could improve the application of immunotherapy in the pre-liver transplantation population, extending beyond the Milan criteria, by utilizing liver function assessments and/or predictors of hepatocellular carcinoma recurrence.

The correlation between irAE onset and ICPI response is evident, yet the specifics of this relationship are not fully understood.

Ongoing research is focused on distinguishing between therapeutic response and adverse effects. A phase II trial was conducted to demonstrate the principle, combining high-dose ipilimumab with or without sargramostim (GM-CSF) in patients diagnosed with metastatic melanoma [111]. Patients treated with GM-CSF exhibited lower levels of toxicity and improved survival compared to those who received only high-dose ipilimumab, while response rates remained comparable between both groups. The mechanism driving this effect is not yet fully understood; nonetheless, a phase III study examining ipilimumab and nivolumab, with or without GM-CSF, is presently in progress (NCT02339571). IL-6 functions as a cytokine that could represent a supplementary target. A recent study analyzed RNA from patient-matched normal colonic tissue and colitis tissue resulting from immune-related adverse events [112]. Differences in gene expression were examined between normal and colitis tissue, along with baseline and on-treatment tumor biopsies from patients who responded to ipilimumab compared to those who did not. In tissue from patients with IRAE-induced colitis, IL-6 showed the most significant differential upregulation when compared to normal colonic tissue. IL-6, in conjunction with various other genes that are differentially upregulated in colitis tissue from patients, did not show a significant increase in responding tumors. IL-6 was recognized as the gene that exhibited differential upregulation in tumor tissue from patients who did not respond. The researchers suppressed IL-6 in conjunction with CTLA-4 in murine models, leading to significant tumor reduction that surpassed the outcomes seen in mice treated solely with anti-CTLA-4 antibodies. To date, there has been no clinical testing of anti-IL-6 directed therapy in combination with ICIICPIs. A clinical trial involving patients with metastatic melanoma has been terminated. It explored the combination of nivolumab and ipilimumab with the alpha 4 beta 7 integrin antagonist antibody vedolizumab and the human chemokine receptor 2 antagonist antibody plozalizumab to evaluate the potential for distinguishing anti-tumor activity from autoimmunity [NCT02723006]. The results from the patients involved in this study are still pending publication.

A close relationship can be observed between autoimmunity and the anti-tumor effects triggered by ICPIs. Current oncology research is increasingly concentrating on the possibility of separating these two elements of immune checkpoint inhibitors to maximize advantages while minimizing patient toxicities. irAEs could function as a clinical biomarker indicating the response to immune checkpoint inhibitors, even though they appear during the course of treatment. The occurrence of IRAE associated with ICPIs shows a stronger correlation with the response generated by anti-PD-1 and anti-PD-L1 antibodies than with anti-CTLA-4 antibodies. This could be attributed to the specific diseases for which each agent has received FDA approval, the varying mechanisms of action of the agents, or the length of treatment (for instance, four doses followed by discontinuation for anti-CTLA-4 compared to prolonged treatment for anti-PD-1 or anti-PD-L1). A variety of inquiries remain concerning the interplay of irAE characteristics, such as site, severity, timing of onset, management strategies, and the efficacy of ICPIs. Additional meticulously structured studies are essential to clarify the influence of irAE characteristics on ICPI response in patients.

Post-LT immunosuppression challenges following neoadjuvant immunotherapy

The complex features of human cancer immune biology have led to a restricted understanding of how immune checkpoint inhibitors operate in liver cancer. Various factors affecting cancer immunity triggered by distinct immune checkpoint inhibitors have been recognized through murine models and ex vivo evaluations of responsive cancer lesions. Shifting these treatments to the pre-liver transplantation setting presents challenges, as antitumor surveillance and graft tolerance are opposing factors that need to be considered concerning patient outcomes [113, 114].

Immune checkpoint inhibitors exhibit distinct mechanisms of action that could hold significant clinical relevance in the setting of post-liver transplantation. Many immune ICPIs target the PD-1/PD-L1 axis, a crucial regulatory mechanism for maintaining tolerance, which is heightened in the microenvironment of immunogenic tumors. PD-1 blockade is thought to enhance anti-improve responses by activating tumor-infiltrating effector T cells. CTLA-4 serves as an immune checkpoint target in the treatment of HCC, influencing T-cell proliferation during the early phases of the immune response, primarily within lymph nodes. This receptor influences T-cell growth in the early phases of the immune response, promoting the rapid decrease of regulatory T cells through antibody-dependent cellular cytotoxicity.

ICPIs have direct immunomodulatory effects and are often used in combination with other anti-cancer therapies. Angiogenesis plays a recognized role in the advancement of HCC and its capacity to escape the immune response [115]. Vascular endothelial growth factor (VEGF) serves as a target for the medications sorafenib, lenvatinib, regorafenib, and cabozantinib. Inhibiting VEGF enhances the infiltration of cytotoxic T and natural killer cells, impedes the activation of regulatory T cells (Tregs), and diminishes the immunosuppressive characteristics of myeloid cells [116]. Assessing the impact of various immunological conditions on the success of organ engraftment poses a significant challenge in the field of immunotherapy for individuals awaiting liver transplantation [117].

The impact of various post-liver transplantation immunosuppressive regimens on systemic antitumor immunity and long-term immune memory introduces further complexity [118]. Immunosuppressive therapy aims to adjust adaptive immune responses and may lessen the long-term effects of immune checkpoint inhibitors before liver transplantation. It is crucial to differentiate between anti-allogenic responses and antitumor immune activity in liver transplantation to advance the creation of targeted therapies or protocols that enhance the survival and function of tumor-specific T-cell effectors while ensuring organ tolerance [32, 119].

DISCUSSION:

Patients with advanced hepatocellular carcinoma typically contraindicate liver transplantation; however, certain individuals may achieve a robust and enduring complete response following immunotherapy. The rising incidence of HCC, along with the widespread implementation of immunotherapy as the standard treatment for advanced HCC, suggests that an increasing number of patients receiving ICPIs may unexpectedly qualify for LT. Case reports demonstrate successful liver transplantation

in patients exhibiting notably durable responses to ICPI therapy [50, 67] Table 2. Ongoing clinical trials are establishing a foundation for the standardization of ICPI use across oncology populations, extending beyond HCC.

Results from the EMERALD-1 provide substantial evidence for the effectiveness of immunotherapy in downstaging HCC. EMERALD-1 was not explicitly designed to examine LT; however, the patient cohort, primarily consisting of individuals with intermediate-stage HCC, along with the non-ICPI treatment employed (TACE), reflects the pre-LT population that undergoes LRT for downstaging or minimizing the risk of waitlist dropout. Consequently, sound conclusions can be drawn regarding the enhancement of HCC treatment efficacy through immunotherapy in the pre-LT cohort. Recent data indicate that the pathological response, characterized by the degree of non-viable tumor in resection specimens following immune checkpoint inhibitor treatment, is associated with recurrence-free survival. This finding aligns with existing research on liver resection therapy, suggesting that a more aggressive treatment objective of eradicating viable disease is superior to merely adhering to Milan criteria. EMERALD-1 and other ongoing phase III clinical trials have not shown that neoadjuvant immunotherapy before liver transplantation is safe, especially when it comes to the risk of allograft rejection after the procedure.

Evidence from multiple case reports and series indicates that pre-LT immunotherapy is generally safe. Tabrizian et al. [45] reported on nine patients who underwent liver transplantation following nivolumab monotherapy, noting one instance of mild acute rejection. Wang et al. [68] conducted a comprehensive study with 16 patients undergoing different anti-PD-1 monotherapies. Nine patients exhibited signs of acute rejection, as evidenced by elevated liver tests rather than histological findings. No instances of graft loss were observed. Research shows that more than 60 patients have received immunotherapy before liver transplantation, with three instances of graft loss noted in patients who were administered immune checkpoint inhibitors within 90 days of the surgery [69]. Tabrizian et al. presented findings from a multicenter study involving 80 patients with HCC who received treatment with ICPI. Of these patients, 30 had undergone liver transplantation before the study abstract was even published. A washout period does not ensure total safety. The literature indicates that most patients underwent anti-PD-1 monotherapy, whereas one of the two standard immunotherapy regimens (STRIDE) includes a combination of anti-CTLA-4 and PD-L1, potentially heightening the risk of immunologic complications [120]. Though there are also serious limitations to take into consideration when evaluating the data from these studies. All ICPI trials exclude patients with autoimmune diseases; thus, caution is necessary concerning neoadjuvant immunotherapy before liver transplantation in individuals with autoimmune hepatitis, given the anticipated heightened risk of disease flare and post-transplant rejection [121].

Surgical resection has been the preferred method for treating early-stage HCC, while ablation therapy is appropriate for patients with solitary lesions or early-stage HCC. Approximately 70% of patients experience recurrence within a five-year timeframe. Researchers are currently studying adjuvant immunotherapy, such as IMbrave050 and

CheckMate 9DX, following resection or ablation. The IMbrave050 study, a phase III clinical trial, demonstrated that adjuvant therapy with atezolizumab and bevacizumab outperformed surveillance alone in terms of progression-free survival. The brief follow-up duration suggests that the observed progression-free survival advantage may not be enduring. A phase II trial of adjuvant sintilimab showed comparable outcomes, indicating enhanced progression-free survival. The existing oncology society guidelines do not provide recommendations concerning the role of adjuvant immunotherapy based on these trials. The data support existing evidence for the use of immunotherapy following surgical resection in select patients with HCC. The application of post-resection or ablation data in the transplant context may be unsuitable due to the ambiguous impact of immune checkpoint inhibitors on tumor surveillance during immunosuppressive treatments after liver transplantation.

Current research is evaluating the safety and efficacy of neoadjuvant immunotherapy in patients undergoing preparation for liver transplantation. ESR-20-21010 is a single-arm, phase II trial that evaluates the STRIDE regimen in patients awaiting liver transplantation who fulfill UCSF criteria for tumor burden, primarily focusing on the assessment of post-transplant rejection. Participants in ESR-20-21010 will undergo STRIDE treatment for a maximum duration of 4 months, following a minimum washout period of 72 days prior to LT. The PLENTY trial is a single-center study examining the efficacy of pembrolizumab in conjunction with lenvatinib, a tyrosine kinase inhibitor, in patients awaiting liver transplantation with a tumor burden surpassing the Milan criteria. Recurrence-free survival is the primary objective, with AEs, including rejection, classified as secondary objectives. Participants must have a minimum washout period of 42 days prior to receiving pembrolizumab. The ImmunoXXL study (NCT05879328) is a multicenter, observational, prospective, single-arm investigation conducted in Europe. This study looks into how well LT works for people with HCC who have had a partial or complete response to atezolizumab and bevacizumab that lasts for more than three months. The objective is to attain a post-transplant survival rate of 60% or higher, evaluated using the Metroticket 2.0 calculator. Patients exhibiting extrahepatic spread or macrovascular invasion are ineligible for consideration. A minimum washout period of 30 days before liver transplantation is necessary.

The studies in question focus on neoadjuvant immunotherapy related to downstaging strategies, as evidenced by their inclusion criteria: ImmunoXXL (which exceeds up-to-seven criteria), PLENTY (which surpasses Milan criteria), and ESR-20-21010 (which adheres to UCSF criteria). The Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) is a collaborative effort among US centers that prospectively examines the effectiveness and safety of immunotherapy in achieving downstaging and minimizing dropout risk in high-risk Given the notable prevalence of downstaged patients encountering waitlist dropout or being classified as “understaged” (for instance, when tumor burden exceeds T2/Milan criteria) based on explant pathology, MERITS-LT has implemented a protocol for high-risk patients to be treated with either atezolizumab combined with bevacizumab or STRIDE after downstaging. Patients with

residual or recurrent disease following downstaging in the MERITS-LT workflow receive immunotherapy. MERITS-LT restricts candidate eligibility to individuals who have shown a more significant disease burden before liver transplantation. This specifically encompasses patients who surpass UNOS downstaging criteria or particular individuals within these criteria recognized as higher risk, including those with elevated AFP levels or multifocal disease. Eligibility for LT is determined after a 12-week washout period, based on the half-lives of atezolizumab, durvalumab, and tremelimumab.

The studies examined concentrate on neoadjuvant immunotherapy in relation to downstaging strategies, as indicated by their inclusion criteria: ImmunoXXL (which exceeds up-to-seven criteria), PLENTY (which surpasses Milan criteria), and ESR-20-21010 (which conforms to UCSF criteria). The Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) is a project that several US centers are working together on to find out if immunotherapy can help treat advanced liver cancer and lower the risk of patients dropping out [43, 70]. Due to the significant occurrence of downstaged patients facing waitlist dropout or being deemed “understaged” (for example, when tumor burden surpasses T2/Milan criteria) according to explant pathology, MERITS-LT has established a protocol for high-risk patients to receive treatment with either atezolizumab in conjunction with bevacizumab or STRIDE following downstaging. Patients exhibiting residual or recurrent disease after downstaging in the MERITS-LT workflow are administered immunotherapy. MERITS-LT limits candidate eligibility to those demonstrating a greater disease burden prior to liver transplantation. This includes patients who exceed UNOS downstaging criteria or specific individuals within these criteria identified as higher risk, such as those with elevated AFP levels or multifocal disease. Eligibility for LT is assessed following a 12-week washout period, which is informed by the half-lives of atezolizumab, durvalumab, and tremelimumab.

Comprehensive investigations into the efficacy and safety of neoadjuvant immunotherapy prior to liver transplantation have left a significant gap in identifying "high-risk" patients with hepatocellular carcinoma. We anticipate the use of pre-LT immunotherapy to remain selective in the absence of substantial evidence demonstrating the clinical superiority of neoadjuvant immunotherapy for HCC in patients evaluated for LT over LRT and surveillance. Further comprehensive, large-scale analysis of chronic ICPI treatment utilization and effects, both within and outside the transplant cohort, will be essential for improving the therapy's efficacy in the future. Moreover, significant investment in the application of biomarkers, such as AFP values and ctDNA, will be essential for reducing the rates of recurrence and late-stage disease.

CONCLUSION

Immunotherapy is advancing from the treatment of advanced hepatocellular carcinoma (HCC) to the earlier stages of the disease. Clinical data suggest that the combination of TACE and immunotherapy in intermediate-stage HCC results in better outcomes, indicating that integrated ICPI treatment may improve tumor control. This holds important consequences for the use of immunotherapy in the pre-liver

transplantation setting, likely decreasing waitlist dropout rates among high-risk patients and enhancing post-transplant results through comprehensive tumor management. Recent evidence suggests that immunotherapy before liver transplantation is safe. Multiple studies assessing the safety and effectiveness of immunotherapy for patients awaiting liver transplantation are currently underway. Immunotherapy is considered appropriate for pinpointing high-risk patients to enhance the effectiveness of downstaging in instances of advanced tumor burden or to maintain a more lasting response while waiting for liver transplantation. Recent studies hold the promise of transforming practices in transplant oncology, especially with the enhanced use of immunotherapy.

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تقييم توحيد العلاج المناعي المساعد قبل الجراحة في مجموعات سرطان الخلايا الكبدية القابلة لزراعة الكبد

عبد الله إسماعيل[1]، ياسر ريّان[2]، هاشم ريّان[2]، معن عبد الرحيم[1]

[1] قسم أورام الجهاز الهضمي، مركز هيوستن ميثوديست للسرطان، مستشفى هيوستن ميثوديست، هيوستن، تكساس، الولايات المتحدة الأمريكية

[2] شعبة الجهاز الهضمي والكبد، قسم الباطنية العامة، كلية الطب، الجامعة الأردنية، عمّان، الأردن

Received: January 30, 2025

Accepted: February 2, 2025

DOI: https://doi.org/10.35516/jmj.v59i1.3957

الملخص

شهد العقد الماضي تحولاً جذرياً في علاج سرطان الخلايا الكبدية (HCC) المتقدم بفضل العلاج المناعي (Immunotherapy). وقد أسفرت تجارب المرحلة الثالثة الحديثة التي بينت ان العلاج المناعي كعلاج فردي أو مركب في المراحل المبكرة إلى المتوسطة من سرطان الخلايا الكبدية اسفرت عن نتائج مُشجعة، بينما لا تزال دراسات أخرى جارية على هذه الفئة من المرضى. ونظراً للنتائج الإيجابية المستخلصة من هذه التجارب، فقد توسع نطاق استخدام العلاج المناعي ليشمل مرضى في المراحل المبكرة من سرطان الخلايا الكبدية، خاصةً أولئك المؤهلين لزراعة الكبد. تُشجع الأدبيات العلمية الحالية بشكل متزايد على توحيد تطبيق العلاج المناعي المساعد قبل الجراحة في سياق زراعة الكبد. وتُعتبر زراعة الكبد علاجاً شافياً لسرطان الخلايا الكبدية، كما تعيد وظائف الكبد الى طبيعته. يعمل العلاج المناعي قبل الزراعة بفعالية على تخفيض مرحلة الورم (Downstaging) وعلاجه، رغم ما قد يحمله من اعراض مناعية جانبيه. تُعد العراض الجانبية الخطيرة احيانا والمرتبطة بالمناعة مصدر قلق كبير لدى الأفراد المصابين بأمراض الكبد المزمنة، وهم أكثر عُرضة لها، هذا بالإضافة إلى ما تحمله من خطر الرفض الحاد بعد الزراعة. إن الهدف الرئيسي من العلاج المناعي في هذه الفئة هو تحسين فرص الحصول على زراعة الكبد مع الحفاظ على النتائج المطلوبة للنجاح قبل وبعد الزراعة. تستعرض هذه الورقة البحثية المختصرة الأدبيات المعاصرة حول استخدام العلاج المناعي في السياق المساعد قبل زراعة الكبد، واستكشاف الفوائد المحتملة لهذا العلاج المركب، وتلخيص النتائج السريرية الحديثة من التجارب البارزة في علاج أورام زراعة الكبد.

الكلمات الدالة: سرطان الخلايا الكبدية، زراعة الكبد، زراعة الأعضاء لعلاج السرطان، الادويه المثبطة لنقاط التفتيش المناعيه.