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Role of Immunotherapy for Liver and Biliary Tract Cancers in the Peri-Surgical Setting, a review

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ABSTRACT

Primary liver malignancies, specifically hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), present a substantial global health burden with rising incidence and mortality rates. While surgical interventions offer curative potential, most patients eventually require systemic therapy. Traditional treatments, such as kinase inhibitors and cytotoxic chemotherapy, have historically provided limited efficacy and significant toxicity. Recently, immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 and CTLA-4 pathways have revolutionized the management of advanced liver cancers, demonstrating superior overall survival and durable responses in landmark trials such as IMbrave150 and TOPAZ-1.

This review evaluates the biological rationale and emerging clinical evidence for the use of immunotherapy in the peri-liver transplant (peri-LT) setting. In the pre-LT setting, ICIs have shown promise for tumor downstaging and as a bridge to transplantation, with high objective response rates and successful conversion to transplant eligibility in some cohorts. However, the integration of immunotherapy into transplant protocols presents a unique challenge of balancing potent anti-tumor immunity with the need for post-transplant immunosuppression to prevent allograft rejection.

Current data from retrospective series indicate allograft rejection rates between 26% and 28%, which are largely comparable to general transplant populations, though the clinical severity of these episodes, including potential graft loss, remains a concern. The duration of the washout period between the last ICI dose and transplantation is a critical determinant of safety, with longer intervals (typically >30 to 90 days) associated with a reduced risk of rejection. In the post-LT setting, ICIs may be considered for systemic recurrence, though they carry a high risk of rejection, potentially mitigated by biomarkers like graft PD-L1 expression. Standardized, evidence-based guidelines are necessary to optimize the safety and efficacy of immunotherapy in transplant oncology.

I. Introduction

The incidence, morbidity, and mortality rates associated with primary liver malignancies, including hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), are steadily increasing. Projections for 2025 estimate over 40,000 new cases and more than 30,000 cancer-related deaths in the United States alone[1,2]. This significant burden positions primary liver malignancies as the fifth leading cause of cancer death[1,2]. Despite considerable advancements in surgical management and locoregional therapies, 50–60% of affected patients require systemic treatment[3].

Hepatocellular carcinoma (HCC) is widely recognized as an inherently chemotherapy-refractory tumor type. Earlier systemic options, such as kinase inhibitors and anthracyclines[4], offered only modest efficacy, typically resulting in a median overall survival (OS) of approximately 9–10 months[5]. These treatments also pose significant tolerability challenges in patients with underlying hepatic dysfunction[4]. This highlights the necessity for novel therapeutic strategies that can induce robust tumor regression while maintaining a favorable safety profile compatible with the underlying liver impairment frequently associated with primary liver cancers.

The effectiveness of systemic therapy for cholangiocarcinoma (CCA) has been similarly constrained. The combination of gemcitabine and cisplatin, established as the standard of care based on the ABC-02 trial, provided a median OS of approximately 11.7 months[6]. However, this regimen was characterized by low objective response rates (ranging from 20–26%), and its utility was often hindered by dose-limiting, treatment-related toxicities, including nephrotoxicity and myelosuppression, particularly in patients with pre-existing hepatic impairment.

Given the limitations of traditional systemic therapies, immunotherapies (IO) have rapidly emerged as a promising alternative for both HCC and CCA. Landmark clinical trials have redefined the treatment landscape. The IMbrave150 trial led to the FDA approval of atezolizumab plus bevacizumab as a first-line standard of care for advanced HCC[7]. The HIMALAYA trial demonstrated improved and durable OS with the STRIDE regimen (Single Tremelimumab Regular Interval Durvalumab), leading to its FDA approval as a first-line treatment for unresectable HCC, particularly in patients for whom anti-VEGF therapy is contraindicated[8]. For CCA, the TOPAZ-1 trial demonstrated superior OS and a favorable safety profile—with fewer adverse events—when durvalumab was added to standard chemotherapy compared to chemotherapy alone[9]. In the randomized, double-blind KEYNOTE-966 trial, pembrolizumab combined with gemcitabine and cisplatin significantly improved OS compared with chemotherapy alone in advanced biliary tract cancers, with a similar safety profile[10]. Data from CheckMate 040 supported the accelerated FDA approval of nivolumab and ipilimumab for HCC due to impressive objective response rates, prolonged duration of response, and manageable safety profiles compared to historical standard-of-care agents[11]. It was not until most recently, in the phase 3 CheckMate 9DW where nivolumab and ipilimumab received approval as first-line treatment for unresectable HCC[12]. Importantly, IO has been anecdotally associated with sufficient tumor downstaging to facilitate subsequent curative interventions, such as liver resection or liver transplantation (LT).[13]

The objective of this review is to critically evaluate the underlying biological pathways that catalyzed the development of immune checkpoint inhibitors and analyze the emerging clinical evidence supporting their role in the peri-liver transplant setting. This work is highly relevant and timely due to the increasing recognition of transplant oncology as a distinct, specialized discipline focused on optimizing outcomes for patients with primary liver cancer.

II. Immune Checkpoint Inhibitor Biology

IIA. PD-1 AND CTLA-4 PATHWAYS

The Programmed Death 1 (PD-1) receptor and its ligand, PD-L1, alongside cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), represent the most significant therapeutic targets in modern immunotherapy[14,15]. Immune checkpoint inhibitors restore anti-tumor immunity by precisely targeting these key inhibitory pathways that regulate T cell function. The PD-1/PD-L1 axis operates as a peripheral immune switch. When the receptor on activated T cells engages with its ligands expressed on tumor cells or surrounding tissues, it triggers the suppression of T cell proliferation and cytotoxic activity. Blocking this interaction with specific monoclonal antibodies effectively releases this inhibition and restores T cell effector function within the tumor microenvironment[16].

The CTLA-4 pathway operates earlier in the immune response cascade, primarily at the stage of T cell priming within lymphoid tissues, by competing with the co-stimulatory receptor CD28[17]. Agents targeting this pathway block this intrinsic inhibitory signal, which enhances T cell activation and diminishes regulatory T cell-mediated immunosuppression. The combined blockade of both pathways generates synergistic anti-tumor immunity[18,19]. Critically for peri-surgical planning, these agents possess prolonged pharmacokinetic profiles. Agents targeting PD-1, such as nivolumab have a half-life of 25 days[20], and anti-PD-L1 agents such as atezolizumab have a half-life of 27 days[21]. Similarly, the CTLA-4 inhibitors tremelimumab and ipilimumab are characterized by shorter half-lives of 18 days and 15 days, respectively[22,23].

Hepatocellular carcinoma and cholangiocarcinoma effectively evade immune surveillance by exploiting these inhibitory pathways within their highly immunosuppressive tumor microenvironments. In the context of hepatocellular carcinoma, multiple non-neoplastic liver cell types demonstrate upregulation of PD-L1, facilitating interaction with PD-1 on tumor-infiltrating T cells and leading to T cell exhaustion. Concurrently, the expression of CTLA-4 on regulatory T cells and antigen-presenting cells within the liver parenchyma elevates the activation threshold of effector T cells, thereby fostering a pronounced tolerogenic state. These inhibitory effects are significantly compounded by the accrual of immunosuppressive cell populations, alongside elevated expression of accessory co-inhibitory receptors like T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3)[24,25].

III. Evidence for Immune Checkpoint Inhibitors in Primary Liver Cancers: From Palliative Efficacy to Transplant Rationale

Systemic treatment for primary liver cancers has been revolutionized by the introduction of immune checkpoint inhibitors in the palliative setting. Landmark phase III trials have established immunotherapy-based regimens as the standard of care for advanced disease. For instance, the IMbrave150 and HIMALAYA trials demonstrated superior overall survival for patients with advanced hepatocellular carcinoma receiving combination immunotherapies compared to traditional kinase inhibitors[7,26]. Similarly, the TOPAZ-1 and KEYNOTE-966 trials established that adding checkpoint inhibitors to standard chemotherapy significantly improves overall survival in patients with unresectable biliary tract cancers[9,10]. Additional studies, such as CheckMate 040 and EMERALD-1, have further highlighted the ability of these agents to produce durable responses and improve locoregional control[11,27]. Furthermore, the CheckMate 459 trial demonstrated that nivolumab provides a favorable safety profile and improves median overall survival compared to sorafenib as a first-line therapy[28].

Building upon these palliative successes, recent investigations have expanded the use of checkpoint inhibition into the neoadjuvant and adjuvant surgical settings for resectable tumors. Phase Ib and II neoadjuvant trials evaluating agents like nivolumab

and cemiplimab have demonstrated the feasibility of these therapies, with substantial proportions of patients achieving major pathological responses prior to surgical resection[29, 30, 31]. For biliary tract cancers, the ongoing NCT04308174 trial aims to determine if neoadjuvant chemotherapy plus durvalumab can improve resectability and long-term outcomes[32]. In the adjuvant, post-resection space, the IMbrave050 trial for hepatocellular carcinoma and the ACCORD trial for biliary tract cancers both showed significant improvements in recurrence-free survival when immunotherapy was utilized following curative-intent surgery[33,34]

These encouraging outcomes in non-transplant surgical candidates provide a compelling rationale for exploring immunotherapy in more complex clinical scenarios. Specifically, the ability of these agents to induce deep pathological responses and robust tumor downstaging has sparked immense interest in their potential as a bridge to curative therapies for patients with high-burden disease. As transplant oncology continues to evolve as a distinct discipline, the crucial next step is evaluating how this potent systemic efficacy translates to the peri-liver transplant setting, where the dual goals of tumor control and allograft tolerance must be carefully balanced.

IV. Safety and Efficacy of Immune Checkpoint Inhibitors Prior to Liver Transplantation

IVa. THE IMMUNOLOGIC DILEMMA AND HEPATOTOXICITY PROFILES

The application of ICIs in patients with HCC and CCA has demonstrated promising oncologic outcomes; however, the safety profile of utilizing these agents in the pre-LT setting remains a significant clinical concern. The integration of IO in the pre-transplant (pre-LT) setting presents a complex therapeutic dilemma. The fundamental goal of IO is to stimulate the host immune system, reversing T-cell exhaustion and enhancing cytotoxic T cell function. Successful liver transplantation mandates long-term immunosuppression to prevent allograft rejection. As IO use expands in liver cancer management, including as a bridge to transplantation, the critical challenge is balancing effective tumor control with necessary transplant safety. The current evidence base is limited to published retrospective single- or multi-center case series describing IO use in the peri-transplant setting, with no published prospective trials available.

In addition to post-LT immunologic risk, ICIs are associated with immune-related adverse events (irAEs) that may limit their utility in the pre-LT setting. Among these, hepatotoxicity is of particular concern in patients with underlying liver disease, as it can necessitate therapy discontinuation and potentially complicate transplant candidacy. In the IMbrave150 trial, treatment discontinuation of at least one regimen component due to adverse events (AEs) occurred in 15.5% of patients receiving atezolizumab plus bevacizumab. Clinically significant hepatotoxicity was a primary driver of these events, with grade 3-4 elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) reported in 7% and 3.6% of patients, respectively[7]. Similarly, data from the HIMALAYA study's STRIDE cohort showed that 13.7% of patients discontinued treatment due to treatment-related AEs (TRAEs), with grade 3-4 AST and ALT elevations occurring in 5.2% and 2.7% of patients. In the CheckMate 040 trial (Arm A), the rate of treatment discontinuation due to TRAEs was higher at 18%, and grade 3–4 TRAEs were observed in 53% of the cohort[26]. For patients with biliary tract cancers, the TOPAZ-1 trial reported that 8.9% of patients discontinued durvalumab due to TRAEs[9], while the KEYNOTE-966 trial found that 15% of patients discontinued any study medication due to TRAEs, with grade 3-4 TRAEs occurring in 70% of the pembrolizumab plus chemotherapy group[10].

IVb. CLINICAL EFFICACY AND DOWNSTAGING SUCCESS

In North America, there are multiple publications illustrating immunotherapy use in the pre-transplant setting. Tabrizian and colleagues conducted a prospective study treating 17 patients with

atezolizumab and bevacizumab. Notably, 16 of the 17 patients were initially outside of the Milan Criteria. The cohort demonstrated an objective response rate of 94% and successful downstaging in 82%. Survival rates at one and three years were 94.2% and 88.2%, respectively, underscoring both the efficacy and safety of the approach, as no severe post-transplant rejection or graft loss occurred[13]. In a 6-center North American study conducted by Tabrizian and colleagues, 117 patients with hepatocellular carcinoma who were evaluated for liver transplant received immunotherapy prior to transplantation[35]. The vast majority, 94%, received concurrent locoregional therapy. Of the 117 patients, 86 (73.5%) exceeded Milan Criteria, and of these, 65 (75.6%) were successfully downstaged. Of the 117 patients initially evaluated, 43 (36.7%) underwent transplantation, including 23 who were initially outside Milan Criteria and successfully downstaged with immunotherapy.

The Asian experience includes several series. In a multi-center, retrospective cohort study by Guo and colleagues, 83 recipients received immunotherapy prior to liver transplantation. Chen and colleagues reported five patients in their series where the median time from PD-1 inhibition to transplantation was 64 days; while none experienced allograft rejection, two had tumor recurrence at three and seven months post-LT[36]. Kulkarni and colleagues included twelve patients treated with atezolizumab and bevacizumab, of whom five underwent transplant. Among these five patients, three experienced wound healing complications, and one succumbed to sepsis. The four remaining transplanted patients had no reported recurrence or allograft rejection at their 10-month follow-up[37]. The integration of immune checkpoint inhibitors into neoadjuvant and downstaging protocols introduces the paradoxical risk of hyperprogressive disease, a phenomenon characterized by accelerated tumor kinetics and reported in approximately 10–15% of hepatocellular carcinoma patients receiving checkpoint blockade[38,39]. Within the specific constraints of transplant oncology, rapid tumor expansion or extrahepatic dissemination can result in immediate and irreversible delisting from the organ waitlist. This risk profile underscores the need for a conservative approach in patients who already meet Milan Criteria and remain stable on the waitlist. For these candidates, conventional locoregional therapies remain the standard of care for bridging, while the use of immune checkpoint inhibitors may be more appropriately reserved for high-burden disease where the potential for successful downstaging justifies the inherent risk of explosive progression.

IVc. ALLOGRAFT REJECTION AND THE CRITICAL WASHOUT PERIOD

The risk of post-transplant rejection has been associated with the duration of the washout period before liver transplantation. Prolonged washout periods are associated with reduced risk of allograft rejection[40]. Nordness and colleagues were the first to report severe graft-related complications associated with checkpoint inhibitor use in proximity to liver transplantation. Their patient received the final dose of nivolumab 8 days prior to transplant and subsequently developed fulminant hepatic necrosis, resulting in mortality despite treatment with high-dose corticosteroids and additional immunosuppressive agents[41]. Aby and colleagues documented acute cellular rejection in a case where liver transplantation was performed only 16 days following the final administration of nivolumab[42]. A 2021 case report described a patient treated with nivolumab who had nonviable disease at treatment completion and underwent transplantation 5 weeks after the final nivolumab dose, yet a liver biopsy performed on post-operative day 10 demonstrated acute cellular rejection[43]. An earlier case series published by Tabrizian and colleagues documented nine total patients who received immunotherapy prior to transplantation. With a median washout period of 41 days, one of the nine patients experienced acute cellular rejection[44]. Conversely, the Schnickel and colleagues case series of five patients who received nivolumab detailed severe complications: two patients, with cessation intervals of less than three months, developed acute cellular rejection that progressed to allograft necrosis, and one patient

suffered cholestasis[44, 45]. The initial two patients detailed in the Rudolph and colleagues case series were treated with immunotherapy prior to liver transplantation. One patient had a washout period of 55 days and subsequently developed graft-versus-host disease. The second patient had a washout period of just 13 days and experienced biopsy-proven acute cellular rejection[46]. Liu and colleagues reported nine cases of patients treated with immunotherapy, four of whom proceeded to transplantation. Of those transplanted, one patient developed rejection at 5 weeks, 9 weeks, and 5 months post-transplantation, a presentation deemed not to be immunotherapy-induced given the late onset[47].

Further literature demonstrates that shorter washout periods are associated with elevated rejection risk. In the European-conducted systematic review and individual patient data meta-analysis by Rezaee-Zavareh and colleagues, 91 patients received immune checkpoint inhibitors prior to liver transplantation. Among them, 24 patients (26.4%) developed allograft rejection. Both age and washout duration were independently associated with rejection risk. Specifically, increasing age was protective, while a longer washout period significantly reduced the likelihood of rejection. Notably, allograft rejection did not adversely affect overall survival. Based on multivariable Cox regression adjusting for age and washout duration, the investigators estimated that a median washout interval of 94 days was required to achieve a rejection probability of 20% or less[40]. The joint retrospective study between North America and Europe of 119 hepatocellular carcinoma patients by Moeckli and colleagues stratified washout periods as less than 30 days, 30 to 50 days, and greater than 50 days. Of these 119 patients, 24 (20.2%) experienced acute cellular rejection. On univariate analysis, patients in the less than 30 days and 30 to 50 days groups had significantly higher rejection rates compared to those in the greater than 50 days group[48]. A multicenter retrospective analysis in China also demonstrated that longer washout periods, defined as greater than 30 days, represented an independent protective factor against rejection[49].

These data demonstrate that the allograft rejection rates associated with pre-transplant immunotherapy, ranging from 26.4% to 27.7% in current clinical series, are largely comparable to the 15-25% rejection incidence typically reported in the general liver transplant population[50]. While this comparison suggests that immunotherapy may not significantly elevate the absolute frequency of rejection, the clinical severity of these episodes remains a profound concern, as they can potentially lead to irreversible graft loss and recipient death. Consequently, implementing an appropriate washout period is essential to mitigate these risks and ensure that immunotherapy remains a safe and viable option in the pre-transplant setting. The pharmacokinetic properties of these agents are a critical consideration in this timing; given that most immunotherapy agents demonstrate a half-life of approximately 15 to 30 days, including nivolumab (25 days), atezolizumab (27 days), tremelimumab (18 days), and ipilimumab (15 days), therapeutic antibody levels and T-cell activating effects can persist for several months following the final dose. Currently, no consensus exists regarding an optimal washout period, and reported intervals have varied considerably across studies. Therefore, while immunotherapy has demonstrated feasibility as a bridging or downstaging therapy, there is a critical need to establish standardized, evidence-based guidelines for the peri-transplant washout period.

V. Use of Immunotherapy in the Post-Transplant Setting

Recurrences are reported to occur in substantial minorities of patients with hepatocellular carcinoma and cholangiocarcinoma within three to five years post-transplant. Recurrence risk is influenced by specific risk factors, particularly pre-transplant tumor size and number. In a large retrospective cohort study of more than 2,600 patients with hepatocellular carcinoma, recurrence rates were 20.6% in those who underwent downstaging prior to transplant, 13.3% in those who remained within Milan criteria throughout, and 41.1% in patients who never

underwent downstaging[51]. In a multicenter study across 12 high-volume transplant centers, patients with perihilar cholangiocarcinoma who received neoadjuvant therapy followed by liver transplantation demonstrated 78% and 65% recurrence-free survival at one and five years, respectively[52]. In a systematic review of 18 studies on intrahepatic cholangiocarcinoma encompassing 355 patients, the pooled one-, three-, and five-year recurrence-free survival rates were 70%, 49%, and 38%, respectively[53].

Recurrences confined to the hepatic allograft may be managed with surgical resection and/or locoregional liver-directed therapies[54]. For extrahepatic recurrences, sorafenib remains the first-line treatment and has been approved since 2008[55], with some studies demonstrating improved 1-year survival with sorafenib compared to standard of care[56]. Given that IO has demonstrated superior tumor responses and a more favorable side effect profile compared to sorafenib in the palliative setting, it may theoretically represent an attractive option for treating systemic recurrence post-transplant, albeit with inherently high risks.

In a case report by Gassmann and colleagues, a patient experienced extrahepatic recurrence of hepatocellular carcinoma approximately two years post-transplant. The patient was initially treated with sorafenib but discontinued the medication due to intolerable side effects and disease progression after two months. Subsequent treatment with nivolumab resulted in graft failure, and the patient died 25 days after the first dose[57]. In a case series by Rudolph et al, two patients developed hepatocellular carcinoma recurrences after liver transplantation at 6 and 24 months. Both cases were treated with atezolizumab and bevacizumab. Although neither experienced graft failure, both demonstrated disease progression and died 7 and 9 months after IO initiation[46]. In a case series by DeLeon et al, 7 patients with metastatic cancer after LT who were treated with IO were included in a retrospective review. Two patients experienced allograft rejection, with a median time to rejection of 24 days following IO initiation[58]. These patients with allograft rejection demonstrated PD-L1 expression in their allografts. Among the seven patients, one achieved complete response, 3 had disease progression, and 3 required therapy discontinuation. Median OS and RFS were 1.1 (0.3-21.1) and 1.8 (0.7-21.1) months, respectively[58].

In a review by Xie et al published in 2022, 28 articles were screened and 47 patients who had undergone ICI therapy after LT were identified. Of these 47 patients, 14 (29.8%) demonstrated some degree of tumor response, including complete responders, while 32 (68.1%) experienced disease progression. Allograft rejection was observed in 15 of the 47 patients (31.9%). During the follow-up period, 29 (61.7%) patients died[59]. Similar findings were reported in systematic reviews by Kayali et al[60] and Yao et al[61], which included 52 and 8 patients who received immunotherapy post-LT, respectively. Acute allograft rejection occurred in 15 (28.8%) and 2 (25%) patients in these respective studies.

Although allograft rejection and loss represent significant risks when treating recurrence with IO, patient selection and predictive biomarkers may mitigate rejection risk and extend post-recurrence survival. In a single-center prospective study,[62] 20 patients who had undergone LT and developed recurrent/metastatic disease were selected to receive IO after demonstrating unresponsiveness to locoregional and systemic therapy. Prior to therapy initiation, liver biopsies confirmed that all 20 patient allografts were negative for PD-L1 expression by immunohistochemistry. Acute rejection occurred in 15% of patients, suggesting that PD-L1 expression status may serve as a reasonable biomarker for selecting post-LT patients in whom PD-1 inhibitors can be more safely utilized[62].

Discussion

In the palliative setting, immunotherapy has improved outcomes for HCC and CCA patients, demonstrating superior response rates, progression-free survival, and OS compared with prior systemic therapy trial results. Landmark clinical trials including IMbrave150, TOPAZ-1, and Checkmate 040 led to FDA approval of

these agents for advanced HCC and CCA. Emerging evidence also suggests that these therapies may represent viable options for downstaging unresectable tumors, enabling patients initially outside transplant criteria to become eligible candidates for LT. However, their incorporation into transplant protocols requires careful evaluation of timing and safety considerations.

In the pre-LT setting, the safety of ICI use appears largely dependent on the washout period, which is defined as the interval between the final ICI dose and the date of transplantation. Case series have consistently demonstrated that shorter washout periods, particularly those less than 30 days, are associated with severe and occasionally fatal rejection events that often remain refractory to high-dose immunosuppression. Conversely, extended washout periods, exceeding 50 days in some cohorts, significantly mitigate this risk. This specific window is supported by pharmacokinetic modeling of nivolumab and pembrolizumab, which demonstrates that a 50-day washout allows for receptor occupancy to fall below the threshold required for sustained T-cell activation. The absence of standardized washout periods across studies underscores the critical need for consensus guidelines establishing best practices regarding immunotherapy use in the pre-LT setting.

The integration of immune checkpoint inhibitors into neoadjuvant and downstaging protocols introduces the paradoxical risk of hyperprogressive disease, a phenomenon characterized by accelerated tumor kinetics and reported in approximately 10–15% of patients with hepatocellular carcinoma receiving checkpoint blockade. Within the specific constraints of transplant oncology, rapid tumor expansion or extrahepatic dissemination can result in immediate and irreversible delisting from the organ waitlist. This risk profile underscores the need for a conservative approach in patients who already meet Milan Criteria and remain stable on the waitlist. For these candidates, conventional locoregional therapies remain the standard of care for bridging, while the use of immune checkpoint inhibitors may be more appropriately reserved for high-burden disease where the potential for successful downstaging justifies the inherent risk of explosive progression.

Despite the theoretical benefits of immunotherapy in the post-transplant setting, tumor responses and patient outcomes remain poor. While some patients have achieved partial or even complete responses to therapy, durable tumor control remains uncommon. In systematic reviews, fewer than one-third of patients demonstrated a radiological response. The majority of patients either experienced rejection or died. Disease progression was the most common outcome, even among patients who did not experience allograft rejection. Given both the inherent rejection risks and limited response rates, immune checkpoint inhibitor use in the post-transplant setting should be considered only in highly selected patients and with close monitoring. Clinical experience requires further validation of predictive biomarkers to identify patients who may safely undergo therapy. Limited studies have described higher rejection risk in patients whose allograft biopsies demonstrated PD-L1 expression, whereas PD-L1-negative allografts were more likely to tolerate exposure with reduced rejection rates. Prospective, biomarker-driven studies incorporating donor allograft profiling may be essential to determine whether these agents can be safely integrated as a treatment strategy for cancer recurrence after liver transplantation.

Recent evidence suggests a potential mechanistic synergy between pre-LT immunotherapy and post-transplant mTOR inhibition. This relationship is underscored by the capacity of mTOR inhibitors to antagonize the PI3K/Akt/mTOR signaling axis, a pathway frequently dysregulated and upregulated in HCC. Therefore, patients with pre-LT exposure may benefit from an early transition to mTOR inhibitor-based regimens[63]. This strategy offers a dual-therapeutic advantage of providing necessary immunosuppression to preserve allograft integrity while simultaneously maintaining secondary oncologic vigilance through its intrinsic anti-proliferative properties[64]. Additionally, clinical

outcomes in the hematologic setting demonstrate that the immunological volatility induced by neoadjuvant programmed death-1 inhibitors can be effectively mitigated. In patients undergoing allogeneic hematopoietic cell transplantation following blockade, the implementation of post-transplant cyclophosphamide has been shown to reduce the incidence of severe graft-versus-host disease and improve recurrence-free survival. Post-transplant cyclophosphamide exerts its effect by selectively depleting rapidly proliferating, alloreactive T-cells responsible for hyper-acute rejection while preserving regulatory T-cell populations. Given these successes, investigating the feasibility of adapted protocols in liver transplantation represents a logical and necessary next step in improving surgical safety and graft tolerance.

Moving forward, substantial knowledge gaps must be addressed before immune checkpoint inhibitors can be safely and effectively integrated into transplant oncology clinical practice. Prospective multicenter studies are needed to define optimal washout periods and establish standardized protocols for the pre-transplant setting. Biomarker-driven approaches to patient selection are required in the post-transplant setting, including assessment of allograft PD-L1 expression. In addition to clinical trial enrollment, real-world registries and collaborative efforts are essential to achieve adequate statistical power and inform the development of consensus guidelines.

Conclusion

Immunotherapy has transformed the treatment landscape for advanced liver cancers in the palliative setting. Its integration into the LT setting represents a critical yet challenging advancement. In the pre-LT setting, washout period duration is the most critical safety determinant, with shorter intervals associated with fatal rejection and extended intervals demonstrating improved safety profiles, though standardized guidelines remain lacking. Post-LT use of ICIs has yielded limited and often poor outcomes, highlighting the inherent challenge of balancing antitumor efficacy with allograft rejection risk. Preliminary evidence suggests that donor graft PD-L1 expression may identify patients at elevated risk for rejection, though this remains an area requiring further investigation. Prospective studies, multicenter registries, and biomarker-driven approaches will be essential for generating the evidence necessary to establish consensus protocols.

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