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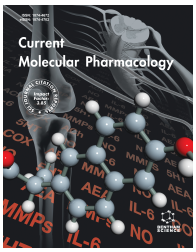

REVIEW ARTICLE

Mechanism, Potential, and Concerns of Immunotherapy for Hepatocellular Carcinoma and Liver Transplantation

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Abstract:

In the last decade, immunotherapy (IT) has revolutionized oncology and found indications in many cancers, including hepatocellular carcinoma (HCC). In HCC, IT has become the leading systemic therapy for advanced diseases. At the same time, it carries the promise of being a valuable therapy in other settings, including intermediate-stage and unresectable disease, as a downstaging or conversion modality. More controversial is the role of IT in relationship to liver transplantation (LT): on one side, it could be a helpful tool to control or downstage HCC before LT or to treat tumor recurrence after LT, while on the other, it carries the risk of graft rejection and graft loss. This review aims to cover these concerns in depth and unravel the current literature.

Keywords: Immunotherapy, Immune checkpoint, Hepatocellular carcinoma, Liver transplantation, Downstaging.

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1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide and represents a major health issue: it is the seventh most common cancer overall and the fourth cause of cancer-related death [1]. Unique in the cancer panorama is the intimate bond between HCC and its underlying predisposing disease. In fact, risk factors for HCC, such as hepatitis viruses, alcohol, and dysmetabolism, all involve chronic insults to hepatocytes and, very often, the concurrent development of liver cirrhosis. This translates into a profound management complexity, which must take into account not only the cancer stage but also the patients' liver and general conditions [2]. HCC tends to be diagnosed at an advanced stage in patients who are not under active surveillance and, therefore, historically, it carries a poor prognosis, as low as 12% 5 years overall survival [3].

Today, clinicians have developed a large array of therapeutic possibilities to contrast HCC and the underlying liver disease. The single most effective curative therapy for HCC remains liver transplantation (LT), which eliminates both the cancer and the HCC-prone liver. With LT, patients with HCC expect survival rates of 80-90%. However, access to LT is limited by donor availability and allocative regulations. Surgical resection and radiofrequency ablation represent the main curative alternatives and remain the mainstay in early disease but have a marginal role in intermediate or advanced-stage HCC [4]. In these situations, Sorafenib, a tyrosine kinase inhibitor (TKI), has been the only drug approved for first-line HCC treatment for a long time [5].

In recent years, the development of immunotherapy (IT) has been of particular interest to HCC clinicians, given the peculiar relationship between the liver and the immune system. In fact, for various reasons, the liver features a unique immune microenvironment and represents an immune-privileged organ [6, 7]. It was thus predictable that boosting anti-cancer immunity in this context might have brought palpable benefits. Recently, trials of IT have proved that IT can be more effective than Sorafenib and revealed the potential of such a strategy [8, 9]. IT drugs have thus conquered their place as first and second-line agents in current treatment algorithms [4]. Furthermore, their success has prompted the enactment of multiple new trials that investigate the benefit of using IT in various disease stages and clinical situations. Among the different scenarios of IT application, its effectiveness in the context of LT is of great interest as the procedure adds

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intricacies both pre- and post-transplantation. In particular, the utility of IT in patients who are candidates for LT or in down-staging advanced HCC, as well as its effects after LT (*i.e.*, in case of recurrent HCC), are currently under investigation.

This narrative review aims to analyze the mechanisms, potential, and concerns related to using immunotherapy for HCC before and after LT.

2. THE HCC MICROENVIRONMENT

The liver plays a special role in immune surveillance due to the peculiar anatomy of its portal circulation, which places it between the hollow digestive organs and the heart. There, it continuously encounters gut-derived pathogens and/or their fragments (antigens). For this reason, the liver's microenvironment is characterized by a unique balance between effective pathogen clearance and tolerance towards non-harmful exogenous molecules. For example, liver dendritic cells (DC) show poor expression of costimulatory molecules and tend to be less efficient immune-activating cells than extrahepatic DCs. Thus, liver resident T-cells are programmed for apoptosis within three days of activation and are depleted by high antigen concentrations [10, 11]. This overall immune-tolerant environment explains why, after LT, rejection of the liver graft is much less of a problem than with other solid-organ transplantations, and spontaneous operational tolerance may be seen [6, 7, 12].

However, in the setting of chronic insults, such as those giving origin to HCC, this tolerogenic milieu may facilitate cancer. Immune deficits in HCC have been implicated in most cell lines. Cytotoxic CD8+ T-cells, for example, despite being the primary infiltrating lymphocyte subtype in HCC, display a markedly attenuated activity with defective production of IFN-γ [13]. Similarly, NK cells may have decreased expression of cytotoxic granules, and an inactive phenotype is associated with HCC progression [14, 15]. These effects may be mediated, in part, by regulatory T-cells (T-regs): FoxP3+ T-regs are increased in HCC, both in the circulation and in the tumor core, and the balance between their presence and that of CD8+ cells correlates with prognosis [16, 17]. Tumor-associated macrophages (TAM) show an M2 phenotype and are associated with lymphocyte depletion, increased vascular infiltration, and multifocality [18, 19]. Subtypes of DCs have been observed to dampen anti-cancer responses through IL-10 production [20, 21], while myeloid-derived suppressor cells (MDSC) may promote tumor progression *via* the production of vascular endothelial growth factor (VEGF), which is a molecule able to induce neo-angiogenesis, a fundamental process for tumor growth. Recently, a proper "tumor-immune barrier" was described by Liu *et al*. [20]. They identified a spatial niche at the tumor margin where hypoxic conditions stimulate the expression of SPP1, and the interaction between SPP1+ macrophages and cancer-associated fibroblasts (CAF) produces extracellular matrix remodeling, inhibiting infiltration in the tumor core [22]. In fact, in pre-clinical models, SPP1 blockade improved immune infiltration and the efficacy of IT [22].

Thus, HCC fosters an environment that is predisposed to favor immune evasion, entailing an abundance of suppressive elements (T-regs, TAMS, DCs, MDSCs, CAFs) and defective cytotoxic responses. Among the mechanisms of effector lymphocyte restraining is the activation of immune checkpoints. These co-inhibitory molecules that negatively regulate T-cell activation include programmed death-1 (PD-1), its ligand PD-L1, cytotoxic T-Lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3, V-domain immunoglobulin suppressor of T cell activation, and T cell immunoglobulin and mucin domain containing-3 [23].

The rationale for the use of immunotherapy for HCC is, therefore, based on the observations that HCC exploits immune checkpoints for immune evasion.

3. MECHANISM OF ACTION OF IMMUNOTHERAPY AGENTS

IT agents stimulate and unleash the immune response to cancer by blocking the co-inhibitory pathways. Among the pathways known, the currently available drugs target either the PD-1/PD-L1 or the CTLA-4 pathways, the so-called immune checkpoints. PD-1 is an inhibitory receptor that is expressed by T cells in conditions of chronic activation [24]. Its binding to PD-L1 starts an intracellular signaling cascade, culminating in T-cell inactivation/exhaustion. PD-L1 can bind to a different receptor, B7-1(CD80), which also initiates similar consequences, including inhibition of cytokine production and proliferation [25]. In HCC, PD-L1 overexpression by neoplastic cells represents a key immune evasion mechanism [26]. CTLA-4 acts in a similar manner, as its high avidity binding to B7-1(CD80) leads to inefficient co-stimulation by CD28 and results in defective T-cell activation in lymph nodes, especially in the presence of "weak" antigens, such as those derived from the self/tumor [27]. In fact, T-regs use this mechanism to induce tolerance/exhaustion in surrounding cells. Fig. (**1**) depicts the exploitation of immune checkpoints by HCC cells and the inhibition of this mechanism by IT.

A combination that has proved successful in HCC treatment is the association of an immune checkpoint inhibitor (ICI) with an anti-angiogenic agent, such as bevacizumab. Bevacizumab is a humanized IgG1 monoclonal antibody that binds to VEGF, neutralizing its activity and preventing its binding to receptors. VEGF mediates neo-angiogenesis and vascular permeability, two features of great importance for HCC, which is a highly vascularized tumor [28]. Furthermore, it appears that VEGF can dampen immune activity inside the tumor in several ways, including the promotion of the expression of PD-1 by CD8+ T-cells [29, 30]. Therefore, the use of ICIs and anti-VEGF molecules appears to produce a potent synergistic effect.

4. IMMUNOTHERAPY IN THE CURRENT HCC TREATMENT ALGORITHMS

Current HCC treatment algorithms include IT, based on high-quality randomized studies with adequate sample size, statistical power, and follow-up. The initial investigation of IT in patients with HCC started with a couple of trials that failed to demonstrate its superiority to sorafenib. Both Nivolumab and Pembrolizumab (anti PD-1 monoclonal antibodies), after being proven efficacious as a second-line agents, were found to

be not superior to sorafenib in large randomized trials on systemic treatment-naïve patients [31]. Later on, IT monotherapy was tested with durvalumab (anti-PD-L1 monoclonal antibody) and tremelimumab (anti-CTLA-4 monoclonal antibody), which appeared to be non-inferior to sorafenib therapy [32]. However, by then, attention had shifted to combination therapy, which had given more significant results. The landmark study IMbrave150 was a phase 3 trial involving 501 patients with advanced HCC and no previous systemic treatment. The aim of this trial was to investigate dual IT therapy with atezolizumab (anti PD-L1 monoclonal antibody) and bevacizumab (anti-VEGF monoclonal antibody) compared to treatment with sorafenib monotherapy [9]. Patients were given either atezolizumab 1200 mg IV and bevacizumab 15mg/kg IV every three weeks or sorafenib at 400 mg twice a day. This trial demonstrated the superiority of the combination regimen, with a 42% decreased mortality risk, a median overall survival of 19.2 *vs* 13.4 months with sorafenib, and improved progression-free survival (PFS) and response rate. Given these excellent results, the combination was therefore approved as first-line therapy and currently represents the standard of care for advanced HCC. Most national and international guidelines, which are mainly based on the Barcelona Clinic Liver Cancer (BCLC) algorithm, consider azetolizumab-bevacizumab the preferred therapy for patients considered for systemic treatment.

This trial started fervor in the field, and several studies involving combination therapies with ICIs have been carried out. Combining ICIs with different mechanisms (*i.e.*, PD-1 and CTLA-4 blockade) has been tested by the HIMALAYA trial, with favorable results [32]. For advanced HCC, the durvalumab-tremelimumab combination improved response rate and overall survival (16.4% *vs* 13.8%) compared to sorafenib. Although the trial did not demonstrate PFS improvement, there is no head-to-head comparison between atezolizumab-bevacizumab and durvalumab-tremelimumab, and therefore, the latter has also been approved as a first-line option. Recently, a long-term follow-up of the HIMALAYA trial was published, confirming significant OS benefit at unprecedented time points (30.7% vs. 19.8% at 3 years and 25.2% *vs* 15.1% at 4 years for durvalumab-tremelimumab *vs* sorafenib, respectively) [33]. Instead, the CheckMate 040 trial resulted in approval of the nivolumab-ipilimumab combination as second-line therapy in patients who presented HCC progression on sorafenib [34]. Nowadays, the combination is being investigated further as a first-line treatment in a dedicated trial (NCT04039607).

Another appealing combination is that of ICIs with TKIs; however, there have not been major breakthroughs to date. In a recently published trial, the combination of lenvatinib and pembrolizumab did not meet the pre-specified significance for improved overall survival and PFS [35].

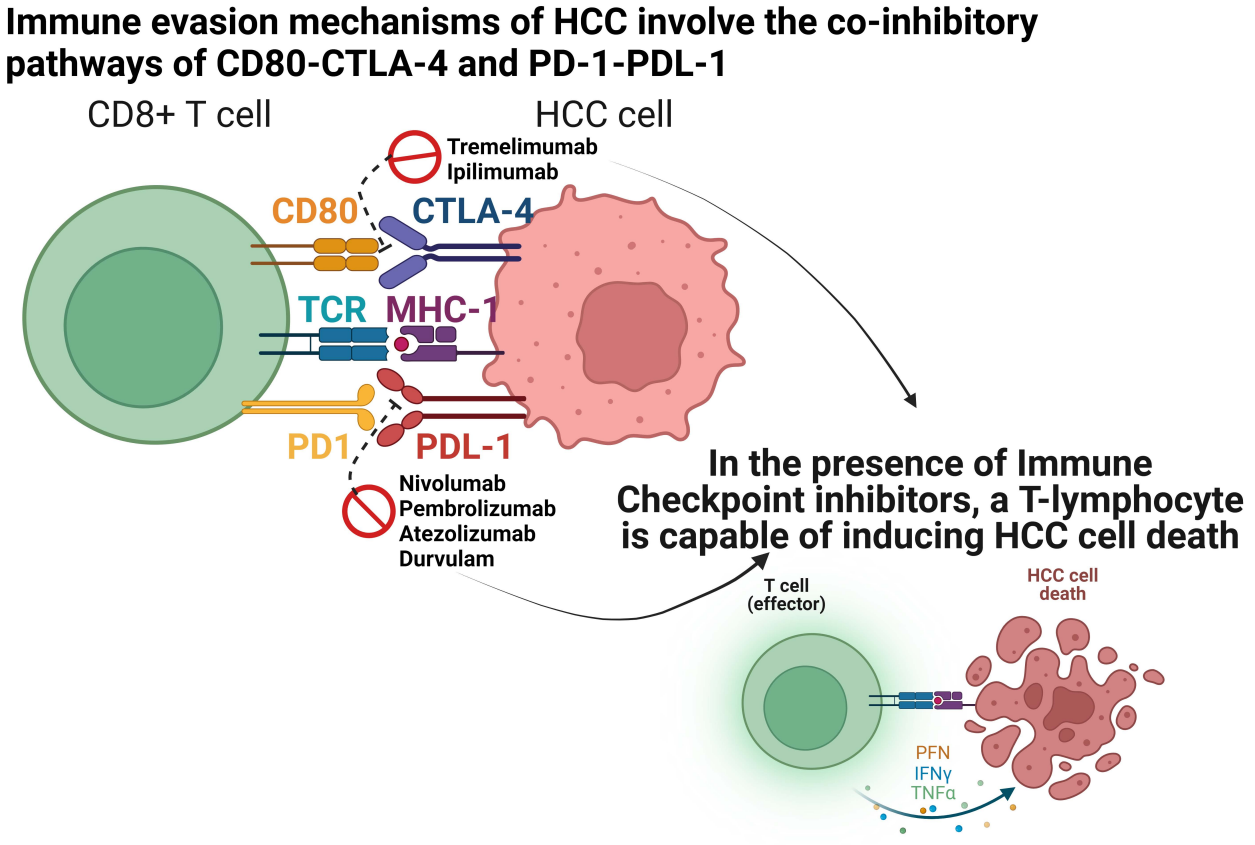

Fig. (1). Exploitation of immune checkpoints by HCC cells and the inhibition of this mechanism by IT.

To summarize, IT combination therapy is efficacious and considered first-line systemic treatment, yet it is currently accepted only for patients with advanced HCC.

5. IMMUNOTHERAPY FOR HCC IN INVESTIGATIONAL SETTINGS

The success of IT in advanced HCC settings has sparked enthusiasm and pushed investigators to verify its advantages in other clinical settings. Among these, IT use in an early and intermediate stage of HCC (according to BCLC staging) is of great interest.

The most widely used HCC staging framework developed by the BCLC takes into consideration not only tumor burden but also liver function and performance status. In the BCLC classification, early-stage patients possess conserved liver function, a good performance status, and low-burden disease, within Milan criteria defined as single nodule or maximum 3 nodules ≤3 cm in size [4, 36]. Of note, in the last few years, this stage-hierarchy-based treatment algorithm has been challenged by the rise and diffusion of a different multiparametric treatment–hierarchy-based approach. This approach entails delivering to our patients the best possible therapy in hierarchical order unless contraindicated, while a multidisciplinary team is in charge of the final treatment decision to avoid possible over-treatment [37]. Independent of stage/treatment approach, patients with low disease burden are mostly directed to surgical resection (whenever possible by a minimally invasive approach, also in advanced liver disease) or LT [38]. Surgical resection guarantees an overall survival of around 70-80%, yet recurrence rates are also reported to be significantly high, being up to 70% [39]. Reducing the probability of recurrence is the goal of IT in this setting. The rationale for such an approach has been validated by Gabrielson *et al*., who described the inverse correlation between the density of T-cell infiltration in the tumor margin and core and the risk of recurrence [40]. In the resectional setting, IT is being investigated in two modalities: neoadjuvant and adjuvant. There are numerous ongoing trials for neoadjuvant IT in early-stage patients who are potentially susceptible to surgical resection (NCT03337841; NCT0351087; NCT03682276). To date, only Kaseb *et al*. have published their phase 2 trial, which yielded interesting results [41]. The trial involved a randomization of patients into neoadjuvant nivolumab *vs* neoadjuvant nivolumab-ipilimumab groups without a control group. In the dual therapy group (14 patients), the median progression-free survival reported was 19.53 months, compared to 9.4 months in the single therapy group (13 patients). Despite the small sample size, these promising results have opened the way for upcoming phase III trials.

IT as adjuvant therapy post-surgical resection for HCC has also aroused interest. The only trial with published results to date, the IMbrave050, has the potential to be another landmark for HCC treatment [42]. In fact, it represents today the only trial of adjuvant therapy with positive results. The atezolizumab-bevacizumab combination (334 patients) significantly improved RFS compared to active surveillance (334 patients). During follow-up, HCC recurred in 33% of patients in the IT group and in 40% in the active surveillance group, and the risk of HCC recurrence was 28% lower in the treatment group (HR 0·72, adjusted 95% CI 0·53–0·98; p=0·012). Atezolizumab-bevacizumab combination appears to have succeeded where sorafenib has failed. However, the follow-up available to date is relatively short, and at the moment of publication, neither group had reached median recurrence-free survival. Longer follow-up will reveal the full extent of the benefit brought about by this potent approach. Other adjuvant IT strategies are being employed in ongoing investigations (NCT03383458; NCT03867084; NCT038 47428).

Intermediate-stage patients have multinodular disease outside Milan criteria, without extrahepatic spread or major vascular invasion, preserved liver function, and good performance status. These patients are usually candidates for trans-arterial chemoembolization (TACE) [4]. TACE provides acceptable outcomes in these patients but is essentially considered a palliative technique. However, there are certain settings in which TACE can be viewed as either a bridging or downstaging technique. TACE can thus be used to reduce the size or number of HCC lesions so as to minimize the chance of drop-out from the LT waiting list for disease progression (*i.e*. bridging), especially in patients who are barely within extended LT criteria or to "convert" patients to a disease burden within accepted LT criteria (*i.e*. downstaging). In all of these above-mentioned settings, IT may represent an adjunctive tool in the hands of expert clinicians.

The addition of IT to TACE in the palliative setting was first reported in a small trial by Duffy *et al*., who tested tremelimumab in combination with locoregional therapy (TACE or ablation) with acceptable safety and feasibility [43]. Whether IT can be established as therapy for intermediate-stage patients as an adjunct or alternative to TACE is still an open question, but there are many trials (NCT04803994; NCT04777851; NCT047126430; NCT04246177; NCT0377 8957; NCT04340193; NCT04268888) with upcoming results which will try to respond soon. In most of these studies, the endpoint has been progression-free survival.

Other investigators instead are evaluating the potential for IT to convert intermediate-stage un-resectable HCC patients to resectable status. Niizeki *et al*. performed a retrospective head-to-head comparison between atezolizumab-bevacizumab and lenvatinib therapy in unresectable HCC: among other results, conversion to operable disease occurred in as many as 8.6% of patients, compared to only 1.9% in the lenvatinib group [44]. Patients in this study were mainly males, with an average age of 72 years, mainly with lesions larger than 3 cm or had more than 5 tumors. Zhu *et al*. explored the efficacy of the combination of ICIs and TKIs: out of 101 patients treated up-front with this strategy, 24 (23.8%) were converted to resectable disease and underwent R0 surgery [45]. In this cohort, patients were younger (median age 52 years), and those who underwent successful conversion tended to have a better baseline performance status while were similar to patients who did not undergo surgery for other characteristics. While these results already appear fascinating, other scholars went further and started researching the potential of combined IT and loco-

regional therapy. Li *et al*. conducted a meta-analysis involving 18 studies comparing TACE and TACE+ICI+TKI in unresectable HCC [46]. Only four studies dealt with triple therapy and included a total of 207 patients [47, 48]. The latter group achieved conversion in 42% *vs* 10% in TACE monotherapy. Another systematic review found similar trends, albeit less optimistic (25% conversion rate) [49]. Of note, all these studies were retrospective and included patients who were deemed unresectable for various reasons, including suboptimal performance status; therefore, the possibility of selection bias was relatively high (*i.e*., using triple therapy in patients who had better performance status and preferentially considering operable these same patients). In another study, factors predicting conversion were scrutinized, and early tumor response appeared to be the only one that independently correlated with conversion [50]. In the same study, successful surgery after conversion was an independent predictor for longer survival. Regarding the safety of surgical resection after triple conversion therapy, there were fewer studies. In the largest case series (83 patients), complication rates appeared acceptable, with overall and major complication rates of 48.2% and 16.9%, respectively [51]. However, in a comparative study by Luo *et al*., 41 patients resected after conversion therapy had significantly higher morbidity than patients who had not undergone such therapy: major complications occurred in 26.8% *vs* 4.9% of cases [52]. Thus, the safety of the procedure must still be further evaluated.

Table **1** summarizes upcoming trials on the use of IT in early and intermediate-stage HCC. IT for bridging or down-staging towards LT is covered in the next section.

Table 1. Ongoing trials on immunotherapy treatment for early or intermediate HCC.

Trial Code	Trial Name	HCC Stage	Setting	Design	Immunotherapy	Sample Size	Primary Endpoints	Follow-up
NCT03337841	Aurora Study	Early; amenable to curative treatment	Neoadjuvant and adjuvant	Prospective Single arm	Pembrolizumab	50	Recurrence-free survival	1 year
NCT03682276	PRIME-HCC	Early	Neoadjuvant	Prospective Single arm	Nivolumab+ Ipilimumab	32	Delay to surgery Safety and tolerability	90 days
NCT03383458	CheckMate 9DX	Early	Adjuvant	Randomised controlled trial	Nivolumab *vs* placebo	530	Recurrence-free survival	49 months
NCT03867084	Keynote-937	Early	Adjuvant	Randomised controlled trial	Pembrolizumab *vs* placebo	950	Recurrence-free survival	72 months
NCT03847428	EMERALD-2	Early, high recurrence risk	Adjuvant	Randomised controlled trial	Durvalumab *vs* Durvaumab + bevacizumab	888	Recurrence-free survival	49 months
NCT04803994	ABC-HCC	Intermediate	Non-curative	Randomised controlled trial	Atezolizumab + bevacizumab *vs* TACE	434	Time to failure of treatment strategy	48 months
NCT04777851	REPLACE	Intermediate ; beyond up-to-seven	Non-curative	Randomised controlled trial	Regorafenib + Pembrolizumab Vs TACE/TARE	486	Progression-free survival	42 months
NCT047126430	TALENTACE	Intermediate	Non-curative	Randomised controlled trial	Atezolizumab + bevacizumab + TACE *vs* TACE	-	Progression-free survival and Overall surviva	
NCT04246177	LEAP-012	Intermediate	Non-curative	Randomised controlled trial	Lenvatinib + pembrolizumab + TACE *vs* TACE	450	Progression free survival	43 months
NCT03778957	EMERALD-1	Intermediate	Non-curative	Randomised controlled trial	Durvalumab + TACE *vs* Durvalumab + bevacizumab + TACE *vs* TACE	600	Progression-free surviva	60 monhts
NCT04340193	CheckMate 74W	Intermediate	Non-curative	Randomised controlled trial	Nivolumab + ipilimumab + TACE *vs* nivolumab + TACE *vs* TACE	765	Adverse events rate	28 months
NCT04268888	TACE-3	Intermediate	Non-curative	Randomised controlled trial	Nuvolumab + TACE/TAE *vs* TACE/TAE	522	Overall survival	24 months

(Table 1) contd.....

Trial Code	Trial Name	HCC Stage	Setting	Design	Immunotherapy	Sample Size	Primary Endpoints	Follow-up
NCT03510871	-	Intermediate;	Downstaging	Prospective Single arm	Nivolumab+ Ipilimumab for 12 weeks before re-evaluation and eventual surgery	40	10% tumor decrease according to RECIST	12 weeks
NCT04425226	PLENTY202001	Intermediate	DownstaginBrifging	Randomised controlled trial	Pembrolizumab + levantinib	220	Recurrence-free survival	48 months

6. IMMUNOTHERAPY IN THE PRE-TRANSPLANTATION SETTING: RATIONALE, PERSPECTIVES, AND CONCERNS

Liver transplantation (LT) is currently the best available therapeutic option for HCC, achieving satisfactory 5 years survival rates as high as 85% [36]. However, the availability of a donor organ limits the offer of such an intervention, and thus, these resources (*i.e.*, grafts) are reserved for patients who would benefit the most from LT. The bulk of these patients are those with good performance status and intermediate tumor burden, often with decompensated cirrhosis and the impossibility of undergoing resection. Several criteria have been established in the attempt to optimize graft distribution, from the strictest (Milan) to more extensive ones. Each "concession" in disease burden carries a corresponding drop in prognosis, as delineated by the Metro ticket concept [53]. Some patients, however, will still be considered ineligible for transplantation. Others will instead progress and drop out from the list while waiting for an organ, and it is in these cases that IT may find a new application.

Currently, downstaging is performed in an effort to reduce tumor burden and present the patient for LT. This strategy usually entails the use of RFA or TACE and, when successful, permits LT with satisfactory oncological results comparable to patients who did not necessitate this process [54]. Similarly, bridging procedures are used after waitlisting in patients at risk for drop-out. In both cases, IT could evidently represent a significant boost to our current capabilities, especially considering the outstanding results reported for "conversion" therapy. However, the LT procedure adds greater complexity compared to surgical resection. In particular, patients will need immunosuppression following LT to avoid graft rejection. This is in striking contrast to the use of IT, which instead activates immunity and is known to carry immune side effects that mimic autoimmunity syndromes, including hepatitis [55]. Obviously, the risk is that of inducing immune-mediated damage to the graft. Indeed, such an inconvenience has been reported in at least four cases where patients suffered acute rejection and hepatic necrosis, culminating in two fatalities and one re-transplantation [56 - 58]. In two cases, IT was suspended only a few days before LT, while in the other two cases, it had been stopped 90 days before transplantation. In fact, Schnickel *et al*. counselled a 90-day washout. Differently, Tabrizian *et al*. reported on 9 patients who were operated <4 weeks after the last nivolumab infusion and who did not develop IT-related complications [59]. Some of these had had multiple transfusions due to considerable blood loss. It is thus conceivable that the risk of rejection correlates with the amount of circulating IT. Depending on the situation in which IT has been given, strategies could vary. If IT is administrated for downstaging, a minimum of 3 weeks to 3 months could be awaited before listing (half-life 3-4 weeks), while for those patients who received IT after waitlisting (*i.e.*, bridging), plasmapheresis could be considered. For the moment, while IT may be considered as a downstaging means for patients with poor prognosis, it should not be regarded lightly in the bridging setting, where it might instead compromise a generally favorable outlook. Other than contemplating a washout phase, it is not clear which patients should be selected for IT downstaging, which are at the highest risk for rejection, and which specific agent could provide the best benefit [60]. So far, Nivolumab has been the most used agent in the downstaging setting [61].

In brief, currently, there is no robust data on IT before LT: the main sources are small case series and case reports, as most clinical trials exclude liver recipients or candidates for LT. To the best of our knowledge, so far, there are 27 cases reported in the literature, of which 4 developed hepatic necrosis (14.8%) [57 - 59, 61 - 64]. Promising data are expected from the PLENTY202001 trial, which is testing lenvatinib-pembrolizumab to downstage HCC exceeding Milan criteria and will hopefully provide quality evidence on the usefulness and safety profile of IT in this setting (NCT04425226). For the time being, IT before LT should only be attempted in the setting of a clinical trial, and considering a wash-out period of 6-12 weeks from the last IT administration appears prudent. Fig. (**2**) depicts an algorithm to consider IT in this setting based on available evidence.

7. IMMUNOTHERAPY IN THE POST-TRANSPLANTATION SETTING: RATIONALE, PERSPECTIVES, AND CONCERNS

Despite optimal survival rates after LT, recurrence of HCC still occurs in around 20% of cases [65]. In these instances, therapeutic options are more limited. Re-transplantation is generally contraindicated, while surgery, although feasible, is limited to low burden disease and only feasible in a minority of patients as most recurrences are extra-hepatic [66]. Although aggressive treatment with resection or ablative techniques appears to improve survival, most patients recur with high-burden disease and are destined for systemic therapy [66]. The prognosis is poor, being around 15 months on average [66].

Again, the potential of IT in this situation is that of improving our patients' survival. However, its use is controversial due to concerns about hepatic rejection and necrosis. The literature is sparse based on some case reports and small case series [67 - 73].

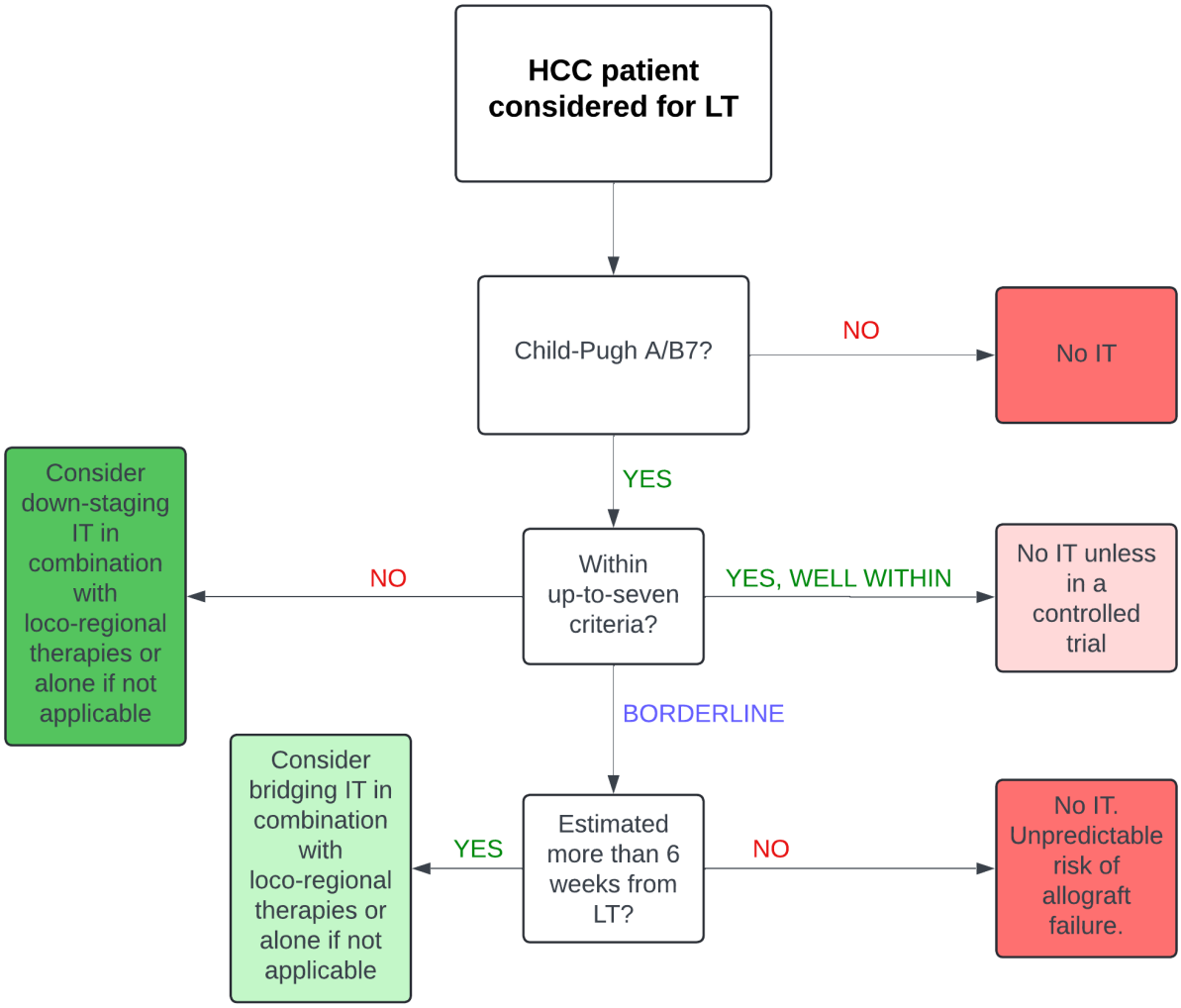

Fig. (2). An algorithm to consider IT.

Au *et al*. identified 28 patients who had been treated with IT post-LT [74]. Results are not exciting in this setting. In fact, the rejection rate was high (32%), causing mortality in a significant percentage of patients (17.8%). This event was more common in patients who were given IT early after LT. However, this observation is of limited utility, as most recurrences occur early in the follow-up. Apparently, rejection happened with all ICIs used (Nivolumab, Pembrolizumab, and Ipilimumab) and at similar rates. Survival rates may be reduced in patients experiencing rejection. A comparison of nivolumab and pembrolizumab appears to favor pembrolizumab in terms of efficacy, but numbers are so small as to be of very limited scientific value. Furthermore, the median overall survival was 7 months, which may not be enough to justify the risks of ICI administration.

Interestingly, a few studies report the successful management of IT after LT, with important lengthening of survival, including two complete responses who remained disease-free for several months (range 10-25). Overall, evidence of the use of ICIs in this setting is absent, and the safety profile reveals a relatively dangerous strategy. Studies to identify those patients who may benefit the most while being less at risk for adverse immunological effects (*i.e*., rejection) are greatly needed. Additionally, the management of immunosuppression in patients treated with IT after LT should be carefully balanced to avoid the risk of rejection.

8. FUTURE PERSPECTIVES

Given the effectiveness of IT for HCC treatment, the most important direction to be taken in future studies is to focus on patient selection for ICI administration in the LT setting (pre- or post-transplant). There are interesting data from an extremely limited sample of patients from the Mayo Clinic group, suggesting that staining of liver allograft biopsies for PD-1 lymphocyte expression may be predictive of rejection, whereas lack of PD-1 staining lymphocytes in the allograft may be associated with a lower risk of rejection [75]. In another study, Szymanska *et al*. confirmed that PD-L1 expression in inflammatory infiltrates may serve as a predictor of rejection [76]. Therefore, it is worth considering the

determination of PD-L1 in liver biopsies of patients who are considered for post-LT IT. Understanding which specific ICI or combination may be more indicated in this setting should also be the subject of further evaluation [75, 77].

CONCLUSION

IT has proven to be a breakthrough in the therapy for HCC, being established as the most effective systemic treatment for advanced disease. Its use in intermediate stage disease is being investigated, and it carries great promise to permit patient downstaging and conversion to resectable disease. The role of IT in candidates for LT is instead more controversial. While it could represent a great advancement in the pre-LT setting, when taking important precautions, such as drug washout, its use in the post-LT setting has not been proven to be safe and should only be considered in experimental settings due to the risk of rejection. Further studies will help refine patient selection and optimize the potential of IT to improve patient outcomes.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: RA; data collection, analysis and interpretation of results: BS; LEC; draft manuscript: BS. Critical review of the manuscript: RA , LT, AC, TMM, GT. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

BCLC	=	Barcelona clinic liver cancer
CAF	=	Cancer-associated fibroblast
CTLA-4	=	Cytotoxic t-lymphocyte-associated protein 4
DC	=	Dendritic cell
ICI	=	Immune-checkpoint inhibitor
HCC	=	Hepatocellular carcinoma
IT	=	Immunotherapy
LT	=	Liver transplantation
MDSC	=	Myeloid-derived suppressor cells
OS	=	Overall survival
PD-1	=	Programmed death 1
PD-L1	=	Programmed death ligand 1
PFS	=	Progression-free survival
TACE	=	Transarterial chemo embolization
TKI	=	Tyrosine kinase inhibitors
T-regs	=	Regulatory t-cells
VEGF	=	Vascular endothelial growth factor

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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