Chapter

Immunotherapy and Hepatocellular Carcinoma

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Abstract

The management of hepatocellular carcinoma (HCC) has been transformed by the incorporation of immune checkpoint inhibitor therapy. Compared to traditional chemotherapy, these regimens have markedly improved outcomes in patients with HCC. Additionally, they are generally well-tolerated in patients with impaired hepatic function. This chapter will review the landmark trials which have paved the way for the use of ICIs in the treatment of HCC and summarize current consensus on best practices regarding their use in this setting. It will also discuss other prospective uses of immunotherapy for the treatment of HCC currently being investigated, including further incorporation of both checkpoint inhibitor and non-checkpoint inhibitor agents into treatment strategies. Furthermore, it will summarize the existing safety and efficacy data regarding the use of checkpoint inhibitors in patients who have previously undergone liver transplant.

Keywords: hepatocellular carcinoma, checkpoint inhibitor therapy, nivolumab, pembrolizumab, sorafenib, Lenvatinib, liver transplant, liver rejection

1. Introduction

Hepatocellular carcinoma (HCC) is estimated to be the sixth most prevalent cancer worldwide and the fourth leading cause of cancer-related death [1]. HCC typically develops in the background of chronic liver disease often in the setting of either chronic infection with hepatitis B or C, alcohol abuse, or metabolic syndrome [2].

The immune system plays a vital role in controlling cancer development and progression [2]. Dysfunction of the tumor and immune system interaction leads to immune evasion through impaired antigen recognition or by tumor creating an immunosuppressive microenvironment [3]. Immune checkpoints are inhibitor molecules expressed by lymphocytes that prevent their overaction. Tumor cells exploit this normal physiological mechanism by expressing these ligands in the tumor microenvironment [4]. The recent emergence of immune checkpoint inhibitors has significantly changed the cancer treatment landscape. These monoclonal antibodies block the interaction of checkpoint proteins with their ligands, preventing the inactivation of T cells [5]. The ligands that are targeted include cytotoxic T lymphocyte-associated antigen (CTLA4), programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), lymphocyte-activation gene 3 (LAG3), etc. [6].

Immune checkpoint inhibitors have had promising results in patients with advanced hepatocellular carcinoma due to the contribution of inflammation and suppression of immune microenvironments to HCC pathogenesis, becoming essential in HCC management [7, 8].

In this chapter, we will review the major immunotherapy trials in patients with advanced HCC in both the firstline and subsequent line setting as well as discuss the mechanism of immune mediated side effects in these patients. We will also discuss the emerging role of immunotherapy in transplant patients.

2. Treatment of hepatocellular carcinoma with immunotherapy

2.1 Firstline treatment

2.1.1 Bevacizumab with atezolizumab

Immunotherapy agents alone or in combination with tyrosine kinase inhibitors (TKI's) or anti-vascular endothelial growth factor receptor (anti-VEGF) therapies have become the cornerstone of treatment for advanced HCC. **Table 1** shows a summary of the main clinical trials involving immune checkpoint inhibitors as both monotherapies and in combination with other systemic therapies used to treat HCC. The combination the PD-L1 monoclonal antibody atezolizumab and anti-VEGF antibody bevacizumab was initially studied in the phase 1b GO30140, which was a multicenter, multi-arm phase 1b study that enrolled patients for first line treatment in nonresectable HCC [9]. The combination of atezolizumab and bevacizumab was compared to atezolizumab alone. In the arm with no randomization (everyone received both atezolizumab and bevacizumab), the objective response rate (ORR) was 36% (95% confidence interval [CI] 26–46) at a median follow-up of 12.4 months with the median duration of response not reached (95% CI 11·8–not estimable), with responses of 6 months or longer observed in 23% of patients. In the comparison arm (atezolizumab and bevacizumab vs. atezolizumab alone), with a median follow-up of 6.6 months for the combination atezolizumab and bevacizumab group and 6.7 months for the atezolizumab alone group, median progression-free survival (PFS) was 5.6 vs. 3.4 months (hazard ratio [HR] 0.55; 80% CI 0.40–0.74; $p = 0.011$). The most common grade 3–4 treatment-related adverse events (TRAEs) were hypertension (5% in combination group, none in monotherapy group) and proteinuria (3% in combination group, none in monotherapy group) [9]. The combination of atezolizumab and bevacizumab in unresectable hepatocellular carcinoma was further studied in ImBrave 150, a phase III clinical trial [10]. In this study, patients with unresectable HCC who had not previously received systemic therapy were randomly assigned to receive either atezolizumab plus bevacizumab or sorafenib until unacceptable toxicity or disease progression. HR for death with atezolizumab and bevacizumab as compared to sorafenib was 0.58 (95% CI, 0.42–0.79; $p < 0.001$) with overall survival (OS) at 12 months 67.2% (95% CI, 61.3–73.1) with atezolizumab and bevacizumab and 54.6% (95% CI, 45.2–64.0) with sorafenib. Median PFS was 6.8 months (95% CI, 5.7–8.3) and 4.3 months (95% CI, 4.0–5.6) in the respective groups (HR for disease progression or death, 0.59; 95% CI, 0.47–0.76; $P < 0.001$). Grade 3 or 4 TRAEs occurred in 56.5% of 329 patients who received atezolizumab-bevacizumab and in 55.1% of 156 patients who received sorafenib. Grade 3 or 4 hypertension occurred

Trial	Comparison and stage targeted	Outcomes	Adverse events
Monotherapy			
CheckMate 040 (Phase I/II) [13]	Nivolumab for advanced HCC, previously treated with or naïve/intolerant to sorafenib	Cohort 1 (dose escalation) = ORR 15%, median OS 15 months Cohort 2 (dose expansion) = ORR 20%	Cohort 1 (dose escalation) – grade 3/4 TRAE rate 25% Cohort 2 (dose expansion) – grade 3/4 TRAE rate 19%
CheckMate 459 (Phase III) [12]	Nivolumab vs. Sorafenib for advanced HCC, sorafenib naïve	ORR 15%, median OS 16.4 months (HR 0.85, p = 0.0752), median PFS 3.7 months	Grade 3/4 TRAE rate: nivolumab 34% vs. sorafenib 49%
KEYNOTE-224 (Phase II) [23]	Pembrolizumab for advanced HCC, previous sorafenib failure/intolerance	ORR 17%, median OS 12.9 months, median PFS 4.9 months	Grade 3/4 rate 26%
KEYNOTE-240 (Phase III) [24]	Pembrolizumab vs. placebo for advanced HCC, previous sorafenib failure/intolerance	ORR 18.3%, median OS 13.9 months, median PFS 3 months	Grade 3/4 TRAE rate pembrolizumab 18.6% vs. placebo 7.5%
KEYNOTE-394 (Phase III) [25]	Pembrolizumab vs. placebo for advanced HCC, previous sorafenib failure/intolerance	ORR 12.7%, median OS 14.6 months, median PFS 2.6 months	Grade 3/4 TRAE rate 14.4% vs. 5.9%
NCT02989922 (Phase II) [26]	Camrelizumab for advanced HCC, previous systemic therapy failure/intolerance	ORR 14.7%, median OS 13.8 months, median PFS 2.1 months	Grade 3/4 TRAE rate 22%
Combination therapy			
IMbrave150 (Phase III) [10]	Atezolizumab + Bevacizumab vs. Sorafenib for advanced HCC, sorafenib naïve	ORR 27.3%, median OS 19.2 months, median PFS 6.8 months	Grade 3/4 TRAE rate Atezolizumab + Bevacizumab 56.5% vs. Sorafenib 55.1%
CheckMate 040 (Phase I/II) [13]	Nivolumab + Ipilimumab (3 dosing arms) for advanced HCC, previous sorafenib failure/intolerance	Arm 1 = ORR 32%, median OS 22.8 months; Arm 2 = ORR 27%, median OS 12.5 months; Arm 3 = ORR 29%, median OS 12.7 months	Grade 3/4 TRAE rate arm 1 53%, arm 2 29%, arm 3 31%
HIMALAYA (Phase III) [14]	Durvalumab + Tremelimumab (D + T) vs. Durvalumab (D) vs. Sorafenib for unresectable HCC	Median OS 16.4 months D + T, 13.8 months in Sorafenib group, 16.6 months D	Grade 3/4 TRAEs in 25.8% (D + T), 12.9% (D), 36.8% Sorafenib
COSMIC-312 (Phase III) [15]	Cabozantinib + Atezolizumab vs. Sorafenib for advanced HCC, no prior therapy	Median PFS 6.8 months in Cabozantinib and Atezolizumab, 4.2 months in Sorafenib group, No statistically significant benefit for Cabozantinib and Atezolizumab vs. Sorafenib (HR 0.90, 96% CI 0.69–1.18, P = 0.438)	Grade 3 or 4 TRAEs 54% Cabozantinib and Atezolizumab, 32% Sorafenib

Trial	Comparison and stage targeted	Outcomes	Adverse events
NCT03006926 (Phase Ib) [18]	Pembrolizumab + Lenvatinib for unresectable HCC	Median OS 22 months, median PFS 8.6 months	Grade 3 or 4 TRAEs 67%
ORIENT-32 (Phase II/III) [21]	Sintilimab + IBI305 vs. Sorafenib for advanced HCC, no prior therapy	Median OS not reached vs. 10.4 months, median PFS 4.6 months vs. 2.8 months	TRAEs hypertension (14% combination, 6% Sorafenib), Palmar-plantar erythrodysaesthesia (none vs. 12%)
CheckMate 040 (Phase I/II) [27]	Cabozantinib + Nivolumab (arm 1) vs. Cabozantinib + Ipilimumab + Nivolumab (arm 2) for advanced HCC, no prior therapy	ORR 17% arm 1, 26% arm 2; median PFS 5.5 months arm 1, 6.8 months arm 2	Grade 3/4 TRAEs 42% arm 1, 71% arm 2

HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression free survival; HR, hazard ratio; TRAE, treatment-related adverse event.

Table 1.
Immune checkpoint Inhibitor Clinical Trials in HCC.

in 15.2% of patients in the atezolizumab-bevacizumab group vs. 12.2% in sorafenib group, grade 3 or 4 aspartate aminotransferase (AST) increase occurred in 7.0% of patients in the atezolizumab-bevacizumab group vs. 5.1% of patients in the sorafenib group; however, other high-grade toxic effects were infrequent [10]. Cheng et al. published updated efficacy and safety data from the IMbrave 150 trial. After a median follow-up of 15.6 months, the median OS was 19.2 months (95% CI 17.0–23.7) with atezolizumab and bevacizumab and 13.4 months (95% CI 11.4–16.9) with sorafenib (HR 0.66; 95% 0.52–0.85; descriptive $p < 0.001$). The median PFS was 6.9 (95% CI 5.7–8.6) and 4.3 (95% CI 4.0–5.6) months in the respective treatment groups (HR 0.65; 95% CI 0.53–0.81; descriptive $p < 0.001$). Grade 3/4 TRAEs occurred in 43% in the atezolizumab and bevacizumab group and 46% in the sorafenib group [11].

2.1.2 Nivolumab

The PD-1 inhibitor nivolumab as monotherapy was compared to sorafenib in the first line setting in the multicenter, phase 3 CheckMate 459 trial in patients with advanced HCC [12]. This was based on the results of CheckMate 040, which was a phase 1/2 non-comparative, dose escalation, and expansion trial with multiple arms for patients with advanced HCC [13]. There was an initial dose-escalation phase followed by dose-expansion for patients who had progressed on prior lines of therapy. During dose-escalation, nivolumab had a manageable safety profile—25% of patients had grade 3/4 TRAEs, 6% had treatment-related serious adverse events (pemphigoid, adrenal insufficiency, liver disorder). Nivolumab 3 mg/kg was chosen for dose-expansion. The ORR was 20% (95% CI 6–28) in the dose-expansion phase and 15% (95% CI 6–28) in the dose-escalation phase. Based on the results of CheckMate 040, CheckMate 459 sought to compare nivolumab monotherapy with sorafenib monotherapy in the first line setting. At a median follow-up for OS of 15.2 months in the nivolumab group and 13.4 months in the sorafenib group, median OS was

16.4 months (95% CI 13.9–18.4) with nivolumab and 14.7 months (95% CI 11.9–17.2) with sorafenib (HR 0.85, 95% CI 0.72–1.02, p = 0.075). ORR was 15% (95% CI 12–19) in nivolumab arm, 7% (95% CI 5–10) in sorafenib arm. The protocol defined significance level was not reached. The most common grade 3 or 4 TRAEs were palmar-plantar-erythrodysaesthesia (<1% in nivolumab group vs. 14% in sorafenib group), AST elevation (6% vs. 4%), and hypertension (0% vs. 7%) [12]. Although first line nivolumab monotherapy did not significantly improve overall survival compared with sorafenib, there was clinical benefit with a favorable safety profile that makes nivolumab monotherapy an option, especially for patients in whom tyrosine kinase inhibitors and antiangiogenic drugs are contraindicated or may have substantial risks.

2.1.3 Other combination therapies

The combination of durvalumab (anti-PD-L1) and tremelilumab (anti-CTLA-4) was compared to sorafenib for first line therapy in the HIMALAYA phase 3 clinical trial [14]. Patients with unresectable HCC were randomized to a single priming dose of tremelilumab with durvalumab (STRIDE), durvalumab monotherapy, sorafenib monotherapy, or tremelilumab and durvalumab. Recruitment to the arm with combination of tremelilumab and durvalumab ceased after a planned analysis showed that this did not differ from durvalumab. Thus, the primary objective was OS for the STRIDE regimen vs. sorafenib and secondary objective was OS noninferiority of durvalumab to sorafenib. Median OS was 16.4 months (95% CI 14.2–19.6) in the STRIDE group vs. 13.8 months in the sorafenib group (HR 0.78; 96% CI 0.65–0.92, p = 0.0035), meeting the primary endpoint. Durvalumab met the objective of OS noninferiority to sorafenib with median OS of 16.6 months (95% CI 14.1–19.1) in the durvalumab group vs. 13.8 months (95% CI 12.3–16.1) in the sorafenib group (HR 0.86; 96% CI 0.73–1.03). Grade 3 or 4 TRAEs occurred in 25.8% (STRIDE), 12.9% (durvalumab), and 36.8% (sorafenib) of patients [14]. This study showed that the STRIDE regimen with a priming dose of tremelilumab and durvalumab had improvements in outcomes with improved tolerability.

Immunotherapy agents have also been studied in combination with TKIs. In the phase III COSMIC-312 study, cabozantinib (multikinase TKI that inhibits MET, VEGFR, RET, etc) and atezolizumab (PD-L1 antagonist) was compared to sorafenib monotherapy and to cabozantinib monotherapy in the first line setting for patients with advanced HCC [15]. The study met the primary endpoint with improvement in PFS: 6.8 months in the cabozantinib and atezolizumab group vs. 4.2 months in the sorafenib group (HR 0.63, 99% CI 0.44–0.91; P = 0.0012. Interim analysis of OS did not show a statistically significant benefit for cabozantinib and atezolizumab vs. sorafenib (HR 0.90, 96% CI 0.69–1.18, P = 0.438). Grade 3 or 4 TRAEs occurred for 54% of patients who received cabozantinib and atezolizumab vs. 32% in patients who received sorafenib. The most common events were palmar-plantar-erythrodysaesthesia (7.9% in patients who received cabozantinib and atezolizumab vs. 8.2% in patients who received sorafenib), hypertension (7.0% vs. 6.3%), AST elevation (6.5% vs. 2.4%), and alanine transaminase increase (ALT) (6.3% vs. 1.9%) [15].

The multikinase inhibitor lenvatinib (inhibitor of VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor alpha, RET, and KIT) is thought to have an immunomodulatory effect on tumor microenvironments and thought to contribute to antitumor activity when combined with immunotherapy. Lenvatinib can inhibit proneoangiogenic and immunosuppressive effects of tumor microenvironments, which would improve the benefit of immunotherapy agents [16, 17]. Finn et al. conducted a phase

1b trial with a combination of pembrolizumab and lenvatinib [18]. 100 out of 104 patients had no prior systemic treatment. At a median duration of follow-up of 10.6 months (95% CI, 9.2–11.5 months), median PFS was 8.6 months and median OS was 22 months. Grade 3 or higher TRAEs occurred in 67% of patients [18]. LEAP-002 is an ongoing clinical trial that is comparing the combination of Lenvatinib and pembrolizumab (PD-1 inhibitor) to lenvatinib plus placebo in the first line setting for advanced HCC [19]. This combination was well-tolerated with promising antitumor activity in patients with advanced HCC in the phase 1b KEYNOTE-524 trial [20].

ORIENT-32 study was a phase 2–3 randomized clinical trial in China that assessed the combination of sintilimab (a PD-1 inhibitor) and a IBI305 a bevacizumab biosimilar versus sorafenib as first-line treatment in advanced HCC [21]. At a median follow-up of 10.0 months, the combination group had a median PFS of 4.6 months (95% CI, 4.1–5.7) versus 2.8 months (95% CI, 2.7–3.2) in the sorafenib arm, HR 0.56, 95% CI 0.46–0.70, $p < 0.0001$. Median OS was not reached for the combination group versus 10.4 months (95% CI 8.5–not reached), HR 0.57, 95% CI, 0.43–0.75, $p < 0.0001$. The most common TRAEs were hypertension (14% of patients in combination group vs. 6% in sorafenib group and palmar-plantar erythrodysaesthesia (none vs. 12%). TRAEs leading to death occurred in 2% of patients in the combination group and 1% of patients receiving sorafenib [21].

2.2 Subsequent treatment

2.2.1 Nivolumab

Immunotherapy agents have also been studied significantly in subsequent lines of therapy. As mentioned previously, CheckMate 040 was a phase 1/2 non-comparative, dose escalation, and expansion trial with multiple arms for patients with advanced HCC [13]. There was an initial dose-escalation phase followed by dose-expansion for patients who had progressed on prior lines of therapy. During dose-escalation, nivolumab had a manageable safety profile—25% of patients had grade 3/4 TRAEs, 6% had treatment-related serious adverse events (pemphigoid, adrenal insufficiency, liver disorder). Nivolumab 3 mg/kg was chosen for dose-expansion. The ORR was 20% (95% CI 6–28) in the dose-expansion phase and 15% (95% CI 6–28) in the dose-escalation phase [13].

Nivolumab (PD-1 inhibitor) monotherapy demonstrated manageable safety, ORR of 14%, duration of response of at least 12 months in 59% of patients, and promising long-term median OS of 15.1 months in patients with advanced HCC treated with sorafenib [13]. The Food and Drug Administration (FDA) granted accelerated approval to nivolumab in HCC based on this study. Further arms of CheckMate 040 then sought to assess the impact of the addition of CTLA-4 immune checkpoint inhibitor ipilimumab to nivolumab in patients with advanced HCC who were previously treated with sorafenib. Patients were randomized 1:1:1 to either nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 240 mg every 2 weeks (arm A); nivolumab 3 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 240 mg every 2 weeks (arm B); or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (arm C). Median follow-up was 30.7 months. Investigator-assessed ORR was 32% (95% CI, 20–47%) in arm A, 27% (95% CI 15–41%) in arm B, and 29% (95% CI 17–43%) in arm C. Median duration of response was not reached (8.3–33.7+) in arm A and was 15.2 months (4.2–29.9+) in arm B, and 21.7 months (2.8–32.7+) in arm C. Median OS was 22.8 months (95% CI,

9.4–not reached) in arm A, 12.5 months (95% CI, 7.6–16.4) in arm B, and 12.7 months (95% CI, 7.4–33.0) in arm C. Any-grade TRAEs were reported in 94% of patients in arm A, 71% in arm B, 79% in arm C, with similar types of events across arms. The FDA granted accelerated approval for this regimen based on this study [22].

2.2.2 Pembrolizumab

KEYNOTE-224, KEYNOTE 240, and KEYNOTE-394 evaluated pembrolizumab in the subsequent line setting in patients with advanced HCC. KEYNOTE-224 was a non-randomized phase 2 trial for patients with advanced HCC who had either progressed or were intolerant of sorafenib. Findings included an ORR of 17% (95% CI 11–26) in patients receiving pembrolizumab. TRAE's occurred in 73% of patients, with grade 3 in 24% and grade 4 in 1% of patients [23]. Based on this study, pembrolizumab was further studied in phase III trials.

KEYNOTE-240 was a randomized, phase III trial in multiple countries that enrolled patients with advanced HCC who had progressed on prior sorafenib to receive pembrolizumab vs. placebo [24]. Results were significant for median OS of 13.9 months (95% CI, 11.6–16.0 months) for pembrolizumab vs. 10.6 months (95% CI, 8.3–13.5) for placebo (HR 0.781; 95% CI 0.611–0.998, p = 0.0238). Median PFS for pembrolizumab was 3.0 months (95% CI, 2.8–4.1 months) vs. 2.8 months (95% CI, 1.6–3.0 months) with HR 0.718 (95% CI 0.570–0.904, p = 0.0022). Grade 3 or higher adverse events occurred in 52.7% vs. 46.3% for pembrolizumab vs. placebo, respectively. Primary end points in this study were OS and PFS, one-sided significance threshold, P = 0.0174 (final analysis) and P = 0.002 (first interim analysis). OS and PFS did not reach statistical significance per specified criteria, but the study showed a favorable risk benefit ratio for pembrolizumab in this population [24]. KEYNOTE-394 was a randomized, phase 3 study conducted in Asia that evaluated efficacy and safety of pembrolizumab vs. placebo as second-line therapy for previously treated advanced HCC [25]. At a median follow-up of 33.8 months (18.7–49.0), pembrolizumab significantly improved OS vs. placebo at 14.6 months for pembrolizumab (95% CI 12.6–18.0) vs. 13.0 (95% CI 10.5–15.1) for placebo (HR 0.79, 95% CI 0.63–0.99, p = 0.0180. Pembrolizumab significantly improved PFS, with median PFS 2.6 months (95% CI 1.5–2.8) for pembrolizumab vs. 2.3 months (95% 1.4–2.8) for placebo (HR 0.74, 95% CI 0.60–0.92, P = 0.0032). ORR was 12.7% vs. 1.3% (estimated difference 11.4%, 95% CI 6.7–16.0, p = 0.00004). TRAEs occurred in 66.9% of patients in the pembrolizumab arm and 49.7% in the placebo arm, including 14.4% vs. 5.9% with grade 3–5 events. This study supported pembrolizumab as a second line option in this patient population [25].

2.2.3 Camrelizumab

Camrelizumab is a PD-1 inhibitor that was investigated in a phase 2 trial in China in pretreated patients with advanced HCC. Patients were randomly assigned to receive camrelizumab every 2 or 3 weeks. With a median follow-up of 12.5 months, ORR was reported in 14.7% (95% CI 10.3–20.2) patients with overall survival probability at 6 months of 74.4% (95% CI 68.0–79.7%). Grade 3 or 4 treatment-related adverse events occurred in 22% of patients; with the most common increased AST (5%), decreased neutrophil count (3%) [26].

The combination of dual immune checkpoint inhibitors tremelimumab (anti-CTLA-4) and durvalumab (anti-PD-L1) was studied in the immunotherapy-naïve population who had progressed on, were intolerant to, or refused sorafenib [28].

Patients were randomized to one of two combinations (tremelimumab 300 mg + durvalumab 1500 mg 1 dose followed by durvalumab every 4 weeks or tremelimumab [arm 1] vs. durvalumab every 4 weeks for 4 doses followed by durvalumab every 4 weeks [arm 2]). These comparative arms were compared to durvalumab monotherapy [arm 3] or tremelimumab monotherapy [arm 4]. Median OS was 18.7 months (95% CI 10.8–NR) in arm 1, 11.3 months (95% CI 8.4–14.6) in arm 2, 11.7 months (95% CI 8.5–16.9) in arm 3, and 17.1 months (95% CI 10.9–NR) in arm 4. ORR was 22.7% (95% CI 13.8–33.8%) in arm 1, 9.5% (95% CI 4.2–17.9%) in arm 2, 9.6% (95% CI 4.7–17.0%) in arm 3, and 7.2% (95% CI 2.4–16.1%) in arm 4. Grade 3/4 treatment related adverse events occurred in 35.1% of patients in arm 1, 24.4% in arm 2, 17.8% in arm 3, and 42.0% in arm 4. This study showed encouraging clinical activity and tolerable safety profile especially with the arm 1 regimen [28].

Combination immunotherapy with TKI or anti-VEGF monoclonal antibody combinations have also been studied in the subsequent line setting in advanced HCC. One of the arms of CheckMate 040 compared the combination of cabozantinib (tyrosine kinase inhibitor that works on VEGF receptor as well as additional targets including c-MET and AXL) and nivolumab (arm 1) to nivolumab, ipilimumab, and cabozantinib (arm 2) [27]. ORR was 17% in arm 1 and 26% in arm 2, median PFS was 5.5 months in arm 1 and 6.8 months in arm 2. Grade 3–4 TRAEs were reported in 42% of patients in arm 1 and 71% of patients in arm 2 leading to treatment discontinuation in 3% of patients in arm 1 and 20% of patients in arm 2. Although the triplet regimen had a higher rate of TRAEs observed, the majority were manageable and reversible with this combination offering another treatment option for patients [27]. Immune checkpoint inhibitors have revolutionized the treatment of many solid tumors, including advanced HCC.

3. Immunotherapy and liver transplant

HCC is unique among solid organ malignancies in part due to the role of transplant in its management. For the select group of patients with unresectable HCC who are found to be appropriate candidates, liver transplant remains the only potentially curative treatment option. In all solid organ transplant patients, modulation of the immune system is necessary post-transplant to prevent graft rejection. Closely titrated and monitored immunosuppressant regimens are used to minimize the risks of both graft rejection and opportunistic infections. The use of both liver transplant and immunotherapy as treatment modalities for HCC gives rise to the question of whether these therapies could interact in a way that increases the risk of graft rejection, blunts the therapeutic effects of immunotherapy, or both. Although research into this field has only recently begun, some trends have begun to arise which may help elucidate the nature of these interactions and help guide future clinicians.

3.1 Treatment of HCC with liver transplant

Patients with locally advanced HCC can be potentially cured by liver transplant. In these cases, total liver resection with replacement of a functional liver acts to eradicate tumor that would otherwise have been unresectable. In order to ensure total removal with transplant is feasible, patients must fit a strict set of criteria to be considered. These criteria, as outlined by Mazzaferro et al. [29] and now known as the Milan criteria, define a subset of patients with more localized disease. According

to the Milan criteria, patients must either one tumor less than or equal to 5.0 cm or up to three tumors none of which exceed 3.0 cm. Additionally, there must be no evidence of vascular invasion or extrahepatic disease. In the original study by Mazzaferro et al., the outcomes of 48 patients whose HCC adhered to these criteria were evaluated. 4-year overall survival following transplant was found to be 75% compared to historic 5-year overall survival rates of 30–40% [29]. 8% of the patients in this series developed recurrent HCC after transplant.

Another, more liberal, set of criteria known as the University of California, San Francisco (UCSF) criteria have been developed which consider patients eligible for orthotopic liver transplant if they had one tumor up to 6.5 cm or no more than three tumors, each 4.5 cm or smaller, with cumulative tumor 8 cm or less. The researchers who developed these criteria, Yao et al., found that patients who were transplanted under this framework had similar survival outcomes to those evaluated using the Milan criteria [30].

Since the development of more stringent criteria, liver transplant has become a mainstay of HCC treatment. Of the roughly 8000 liver transplants performed yearly, about 15–50% are performed on patients with HCC [31, 32]. Yoo et al. evaluated the outcomes of patients who had undergone liver transplant for HCC vs. other indications between 1988 and 2001 [33]. They found a 42.3% 5-year survival rate in patients transplanted for HCC compared to 71.7% in those transplanted for other reasons. However, over time the post-transplant 5-year survival rate in HCC patients had markedly improved from 25.3% between 1987 and 1991 to 46.6% between 1992 and 1996 and 61.1% between 1997 and 2001. A concurrent increase in survival was not demonstrated in patients transplanted for other reasons, supporting the hypothesis that this improvement in outcomes was driven by more stringent selection of patients for transplant rather than improvements in surgical techniques or postoperative management. Other studies have showed 5-year survival rates of roughly 60–80% in patients with HCC who underwent liver transplant, with similar rates seen in transplant patients without HCC [34–36].

3.2 Immunology of liver transplant rejection

Acute transplant rejection can be divided into T-cell mediated rejection (TCMR) and antibody-mediated rejection (AMR) [37]. Of these, TCMR is most common following liver transplant, occurring in 15–25% of patients even with proper use of immunosuppressive therapy [38]. TCMR is characterized by inflammatory infiltration of the portal tracts and perivenular areas with some extension into periportal areas in extreme cases [37]. The predominant cells found in these infiltrates are CD4+ and CD8+ T cells as well as macrophages [39]. In TCMR, alloantigen presentation and T-cell co-stimulation bring about T-cell activation. Activated T cells, mediated by the phosphatase calcineurin, upregulate expression of IL-2 which leads to T-cell proliferation and downstream inflammatory processes [40]. During periods of liver inflammation, MHC class II expression increases in liver endothelial cells, biliary epithelium, and hepatocytes, increasing antigen presentation and T-cell mediated damage at these sites [40]. Of note, there are several additional sources of antigen presenting cells specific to the liver. Liver sinusoidal endothelial cells appear to be capable of antigen presentation to CD4+ and CD8+ T cells. Additionally, the majority of the body's macrophages are present in the liver as Kupffer cells, which are also capable of antigen presentation [39].

Of note, there is some evidence to support the role of the PD-1/PD-L1 axis in preventing TCMR. In mouse models, PD-L1 expression on hepatic dendritic cells was

shown to be necessary to prevent graft failure following liver transplant [41]. Shi et al. demonstrated that T cells which had previously infiltrated an allograft had increased rates of proliferation in response to PD-1/PD-L1 blockade [42]. Bone marrow stromal cells have been investigated as a potential therapy to prevent rejection following solid organ transplantation, owing in part to their expression of PD-L1 [43].

AMR following liver transplant is relatively rare compared to TCMR and is also less common than in other solid organ transplants [44]. AMR is primarily mediated by donor-specific antibodies against non-self class I and II MHC molecules on the surface of the transplanted liver's endothelial cells [40]. AMR is complement-mediated, and is graded by extent of C4d deposition in the portal microvascular endothelia [37].

The mainstay of immunosuppressive therapy for prevention of TCMR is treatment with a calcineurin inhibitor (CNI) [45]. The most commonly-used CNIs are tacrolimus and cyclosporine [46]. By inhibiting calcineurin, they prevent upregulation of IL-2 and therefore T-cell proliferation. In patients for whom CNI monotherapy is insufficient, it is recommended that patients additionally be started on antiproliferative therapy such as mycophenolate mofetil or mammalian target of rapamycin (mTOR) inhibitors such as everolimus [45]. Acute rejection is treated by either temporarily increasing the dose of the CNI in mild cases or with corticosteroids; in severe cases steroid-refractory rejection may be treated with anti-thymocyte globulin [45]. Acute rejection generally resolves with treatment without significant residual graft dysfunction [39].

3.3 Safety and efficacy of immunotherapy in liver transplant patients

Because liver transplant is reserved for patients with localized HCC, and because recurrence is uncommon post-transplant, the overlap of HCC patients who have received checkpoint inhibitor therapy and those who have undergone liver transplant is relatively small. However, for patients who do require both therapies, the simultaneous presence of allogeneic liver graft, chronic immunosuppressive therapy, and increased T-cell immune surveillance by checkpoint inhibitor therapy creates the potential for myriad clinical complications. The foremost concerns in this subpopulation of HCC patients are the prospect of increased risk of TCMR and decreased efficacy of immunotherapy.

3.3.1 Post-transplant treatment with immunotherapy

To date, the combination of immunotherapy and liver transplant is most likely to occur in post-transplant HCC patients who develop recurrence of HCC. While the rate of HCC recurrence post-transplant is low, it is nonzero; recent studies have found that recurrence occurs in about 15–20% of all patients who undergo transplant [47]. The risk of recurrence is elevated with increased immunosuppression with CNIs or corticosteroids, suggesting an effect of standard-of-care immunosuppression and decreased tumor surveillance following liver transplant [45, 48, 49]. Of note, mTOR inhibitors do not appear to confer the same risk [45].

Clinicians have generally been reticent to give immunotherapy in patients with recurrent HCC post-transplant out of concern for instigating TCMR. As such, descriptions of its use in this setting has largely been limited to case reports. In a recent comprehensive literature review, Yin et al. identified 28 patients who received checkpoint inhibitor therapy following liver transplant, 18 of whom were being treated for recurrent HCC [50] (see **Table 2**). Of these 18 patients, 6 (33%)

Author	Age (years)	Indication for LT	Indication for ICI post-LT	Time from LT to ICI (years)	ICI therapy used	Immune suppression at time of ICI	Best response to ICI	Liver toxicity	Time to develop toxicity	Treatment of toxicity	Response to treatment of toxicity
Kumar et al., 2019 [51]	64	HCC	HCC	2	Nivolumab	NA	NA	TCMR	1 week	High dose steroids, ATG, PLEX	Improvement of rejection
Gomez et al., 2018 [52]	61	HCC	HCC	2	Nivolumab	NA	NA	TCMR	1 month	Prednisone	Improvement of rejection
Anugwom et al., 2020 [53]	62	HCC	HCC	5	Nivolumab	Tacrolimus	POD	Immune hepatitis	2 months	Steroids	Worsening of hepatitis
Varkaris et al., 2017 [54]	70	HCC	HCC	8	Pembrolizumab	Tacrolimus	POD	No	—	—	—
Friend et al., 2017 [55]	20	HCC	HCC	3	Nivolumab	Sirolimus	NA	TCMR + AMR	<1 month	Pulse high dose steroids, IVIG	No response, death
Friend et al., 2017 [55]	14	HCC	HCC	2	Nivolumab	Tacrolimus	NA	TCMR + AMR	<1 month	High dose steroids	No response, death
Rammohan et al., 2018 [56]	57	HCC	HCC	4	Pembrolizumab + sorafenib	mTor inhibitor, tacrolimus	CR	No	—	—	—
Amjad et al., 2020 [57]	62	HCC	HCC	1.3	Nivolumab	Tacrolimus	CR	No	—	—	—
DeLeon et al., 2018 [58]	56	HCC	HCC	2.7	Nivolumab	Tacrolimus	POD	No	—	—	—
DeLeon et al., 2018 [58]	55	HCC	HCC	7.8	Nivolumab	MMF, sirolimus	POD	No	—	—	—
DeLeon et al., 2018 [58]	34	HCC	HCC	3.7	Nivolumab	Tacrolimus	POD	No	—	—	—

Author	Age (years)	Indication for LT	Indication for ICI post-LT	Time from LT to ICI (years)	ICI therapy used	Immune suppression at time of ICI	Best response to ICI	Liver toxicity	Time to develop toxicity	Treatment of toxicity	Response to treatment of toxicity
DeLeon et al., 2018 [58]	63	HCC	HCC	1.2	Nivolumab	Tacrolimus	NA	No	—	—	—
DeLeon et al., 2018 [58]	68	HCC	HCC	1.1	Nivolumab	Sirolimus	POD	TCMR	<1 month	NA	NA (died due to POD)
Gassmann et al., 2018 [59]	53	HCC	HCC	3	Nivolumab	Everolimus	POD	TCMR	2 weeks	Steroids, tacrolimus	No response, death
De Toni et al., 2017 [60]	41	HCC	HCC	1	Nivolumab	Tacrolimus	POD	No	—	—	—
Al Jarroudi et al., 2020 [61]	70	HCC	HCC	3	Nivolumab	Tacrolimus	NA	Autoimmune hepatitis vs. graft rejection	2 months	High dose steroids	NA
Al Jarroudi et al., 2020 [61]	62	HCC	HCC	2	Nivolumab	Tacrolimus	POD	No	—	—	—
Al Jarroudi et al., 2020 [61]	66	HCC	HCC	5	Nivolumab	Tacrolimus	POD	No	—	—	—
Kuo et al., 2018 [62]	62	HCC	Melanoma	4.5	Ipilimumab then pembrolizumab	Sirolimus	PR	No	—	—	—
Schvartsman et al., 2017 [63]	35	Biliary atresia	Melanoma	20	Pembrolizumab	Steroids, MMF	CR	Immune hepatitis	1 month	Steroids, MMF	Improvement of hepatitis

Author	Age (years)	Indication for LT	Indication for ICI post-LT	Time from LT to ICI (years)	ICI therapy used	Immune suppression at time of ICI	Best response to ICI	Liver toxicity	Time to develop toxicity	Treatment of toxicity	Response to treatment of toxicity
Ranganath et al., 2015 [64]	59	Cirrhosis	Melanoma	8	Ipilimumab	Tacrolimus	POD	No	—	—	—
Dueland et al., 2017 [65]	67	Melanoma	Melanoma	1.5	Ipilimumab	Prednisone	POD	TCMR	<1 month	High dose steroids, MMF, sirolimus	Improvement of rejection
DeLeon et al., 2018 [58]	63	Cholangiocarcinoma	Melanoma	3.1	Pembrolizumab	MMF, prednisone	NA	TCMR	<1 month	ATG, MMF, tacrolimus, prednisone	Improvement of rejection
Morales et al., 2015 [66]	67	HCC	Melanoma	8	Ipilimumab	Rapamycin	PR	Immune hepatitis	2 months	None	Improvement of hepatitis
DeLeon et al., 2018 [58]	54	HCC	Melanoma	5.5	Pembrolizumab	Everolimus, MMF	CR	No	—	—	—
Chen et al., 2019 [67]	61	Cirrhosis	CRC	2.5	Pembrolizumab	Prednisone (1 mg/kg), tacrolimus	PR	No	—	—	—
Biondani et al., 2018 [68]	54	Cirrhosis	Metastatic squamous NSCLC	13	Nivolumab	Prednisone, tacrolimus, everolimus	POD	No	—	—	—
Lee et al., 2019 [69]	73	HCC	Cutaneous SCC	12	Nivolumab	Everolimus	NA	TCMR + AMR	1 month	High dose steroids, everolimus, MMF	Improvement in TCMR but persistent AMR

Adapted with permission from Yin et al. [48]. HCC, hepatocellular carcinoma; CRC, colorectal carcinoma; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; LT, liver transplant; ICI, immune checkpoint inhibitor; NA, not available; MMF, mycophenolate mofetil; POD, progression of disease; CR, complete response; PR, partial response; TCMR, T-cell mediated rejection; AMR, antibody-mediated rejection; ATG, anti-thymocyte globulin; PLEX, plasma exchange; IVIG, intravenous immunoglobulin.

Table 2.
Characteristics of case reports of patients who received checkpoint inhibitor therapy post-transplant.

experienced TCMR with an additional patient experiencing either acute graft rejection or immunotherapy-related hepatitis. All cases of TCMR occurred within 2 months of starting checkpoint inhibitor therapy. 2 of the 6 patients with proven TCMR also experienced AMR. 3 of 6 of the patients with TCMR died despite treatment with immunosuppressive regimens, including both patients with TCMR and AMR. All of the patients in the series with known PD-L1 positive tumors (4/28, 14%) developed TCMR, reinforcing the potential importance of the PD-1/PD-L1 axis in preventing rejection in liver transplant patients. In terms of mitigating factors, it was noted that the majority of patients who experienced graft rejection were 3 years or less post-transplant and that rejection was rare in late post-transplant patients. Additionally, graft rejection was not observed in any of the 3 patients treated with anti-CTLA-4 therapy alone. This finding is consistent with disruption of the PD-1/PD-L1 axis may be uniquely provocative of TCMR, but as the authors noted the sample size of was very small.

In the same series, of the 11 HCC patients with data regarding response, 2 of 11 (18%) had a complete response while the remaining 9 had progression of disease [50]. It is worth noting that all of these patients had previously received treatment with sorafenib and many had received other lines of therapy as well. The initiation of checkpoint inhibitor therapy after failure of other lines of treatment was likely due to concerns about causing graft rejection and may connote that the sample of patients presented here had more aggressive disease. It is therefore difficult to make definitive conclusions about the efficacy of checkpoint inhibitor therapy in this setting.

3.3.2 Treatment with immunotherapy as a bridge to transplant

Another potential setting for treatment with both liver-transplant and checkpoint inhibitor therapy is in patients who receive immunotherapy as a bridge to transplant. It is not uncommon a patient with borderline tumor characteristics to undergo treatment with locoregional therapy such as trans-arterial chemoembolization or radiofrequency ablation in an attempt to shrink the tumor and qualify them for liver transplant [70]. The effects of these treatments go beyond their impact on tumor size. Extent of tumor necrosis post-therapy is associated with improved relapse-free and overall survival [71–73]. Systemic treatment modalities such as sorafenib have been tried as well. Recently, interest has been raised in the possibility of using immunotherapy to achieve more favorable tumor characteristics and increased tumor necrosis prior to transplant. However, checkpoint inhibitor therapy is characterized by its long duration of response and potential for enhancing immune surveillance long after treatment has been discontinued. Therefore, concerns persist that immunotherapy could cause TCMR post-transplant despite cessation prior to surgery.

In the aforementioned review, Yin et al. identified two cases of patients with HCC who had received immunotherapy as a bridge to transplant [50]. In one case, a patient failed sorafenib and received nivolumab for 2 years before being treated with TACE, at which time his tumor qualified him for transplant using the Milan criteria. He underwent transplant 8 days after his last dose of nivolumab and post-transplant rapidly developed graft rejection that progressed despite high-dose methylprednisolone and rabbit anti-thymocyte globulin before dying on postoperative day 10 [74]. In another case, a patient received 14 months of nivolumab following progression after 1 year of sorafenib at which time he was downstaged and met Milan criteria. He was transplanted 15 weeks after his last dose of nivolumab and at the time of the report, 1 year post-transplant, was doing well with no complications or evidence of recurrence [75].

A single-institution series of 9 cases was reported in which patients with HCC were treated with nivolumab prior to liver transplant [76]. Patients received between 2 and 32 cycles (median 9) of nivolumab with a range of 1–253 days (median 18) between last dose of nivolumab and transplant. Remarkably, only one patient experienced rejection, which was mild in nature and occurred in the setting of subtherapeutic tacrolimus level, and no patients had recurrence of their HCC. In one third of patients, explant showed >90% tumor necrosis. At the time of reporting, all patients were alive with a median of 16 months of follow-up (range 8–23 months) post-transplant [76]. These findings, while still stemming from a small treatment cohort, suggest potential promise in the use of immunotherapy as a bridge to transplant.

These data illustrate a wide spectrum of potential outcomes in patients who receive checkpoint inhibitor therapy either pre- or post-transplant for HCC. Further research is required to identify the subset of patients least likely to experience graft rejection, as well as those most likely to benefit from checkpoint inhibitor therapy despite being on immunosuppression.

4. Immune checkpoint inhibitor toxicity in HCC patients

Checkpoint inhibitors, while generally better-tolerated than conventional chemotherapy, can nonetheless have myriad complications due to autoimmune-mediated damage at various locations in the body. The characteristics of this toxicity profile and its management specific to HCC patients will be reviewed here, as will the clinical implications of checkpoint inhibitor toxicity in this population.

4.1 Challenges specific to HCC patients

Checkpoint inhibitor therapy can cause a number of different organ toxicities, including dermatologic complications, colitis, endocrine dysfunction, and hepatitis, among others. Some cancer types have higher associations with certain immune-related adverse events (irAEs). For instance, melanoma treatment with checkpoint inhibitor therapy is associated with a higher rate of dermatologic toxicities such as vitiligo, while renal cell carcinoma is associated with gastrointestinal toxicities following checkpoint inhibitor therapy [77]. Similarly, treatment of HCC with checkpoint inhibitors appears to be associated with increased rates of hepatitis compared with other cancer types [78]. A major contributing factor to this association is the high rates of underlying liver disease in patients with HCC. Concomitant liver disease such as HBV, HCV, and non-alcoholic steatohepatitis can provide an alternative cause of rising AST and ALT, increase the vulnerability of the liver to further damage, increasing the impact of irAE-related hepatitis when it does develop.

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are common contributors to the development of HCC, and concerns have been raised regarding the potential for both checkpoint inhibitor therapy and treatment of irAEs to cause viral reactivation. In a large recent cohort study, Yoo et al. evaluated rates of HBV reactivation 3465 patients who had received immunotherapy as part of cancer treatment [79]. Among patients positive for hepatitis B surface antigen (HBsAg), HBV reactivation was rarely seen in those with HCC, occurring in only 0.5% of cases. However, in all patients with positive HBsAg rate of HBV reactivation was higher in patients not taking antiviral prophylaxis (6.4%) compared to those who were (0.4%), emphasizing the importance of appropriate antiviral prophylaxis in this group

regardless of HCC status. A literature review by Pu et al. of patients with HBV and/or HCV treated with checkpoint inhibitors identified 89 patients with HBV, 2 of whom (2.2%) experienced reactivation as well as 98 patients with HCV, 1 of whom (1.0%) had an increase in viral load following treatment [80].

While the risk of HBV and HCV reactivation appears to be low in patients treated with checkpoint inhibitor therapy, some of the immunosuppressive medications used to treat irAEs carry increased risk of viral reactivation. In the American Society for Clinical Oncology (ASCO) guidelines for management of irAEs, the use of TNF-alpha inhibitors such as infliximab is recommended for a number of grade III and/or IV toxicities such as colitis, pneumonitis, and inflammatory arthritis that are resistant to steroids [81]. TNF-alpha inhibitors are known to cause HBV reactivation but appear to be generally safe to use in patients with HCV [82, 83]. Mycophenolate has not been associated with HBV reactivation, and could be considered in many cases of patients with chronic HBV experiencing severe irAEs despite corticosteroid therapy [84].

4.2 Immunotherapy toxicity and outcomes in HCC patients

The development of irAEs with checkpoint inhibitor therapy is known to be associated with improved progression-free and overall survival across multiple cancer types [85]. Multiple studies have shown that this trend extends to patients with HCC [86–88]. The relationship between irAE development and prognosis extends to HCC patients who develop high-grade irAEs, and in some studies higher grade irAEs were an even greater predictor of overall survival [87]. Although patients with HCC may be at risk for increased morbidity from irAEs due to underlying liver disease, practitioners should generally attempt to continue treatment whenever feasible, in accordance with the established ASCO guidelines.

5. Conclusion

The landscape of treatment for HCC has been fundamentally changed with the advent of immunotherapy. Despite this shift, patients with HCC often have a unique set of circumstances which predisposes them to toxicities related to these drugs. Additionally, the dual roles for immunotherapy and liver transplant in this population can cause complex interactions and potentially devastating complications. Further research to identify other immunotherapeutic treatment modalities is underway. Additionally, more research will be required to better characterize the treatment toxicities and risks associated with transplant.

Conflict of interest

The authors declare no conflict of interest.

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