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The Promise of Immunotherapy in the Treatment of Hepatocellular Carcinoma

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OVERVIEW

Advanced hepatocellular carcinoma (HCC) has presented a therapeutic challenge. Despite its heterogeneity, which is partially related to its various etiologies, it frequently arises in a background of chronic inflammation, which makes it a potentially excellent candidate for immunotherapeutic approaches. There is evidence of antitumor immunity in HCC as manifested by the cell infiltrate and its association with prognosis, the presence of tumor-associated antigens, and the reports of immune-mediated spontaneous regressions. However, both the liver itself and the tumor environment possess a diverse armamentarium of mechanisms that suppress antitumor immunity. Here, we describe the rationale for immunotherapy in HCC and discuss the emerging clinical data from various immunotherapeutic approaches including checkpoint inhibition, cell therapy, oncolytic viral therapy, and various combinatorial approaches. We also highlight the potential for various modalities to be adapted across different stages of the disease.

HCC has an incidence of over 500,000 new cases globally and is the second most frequent cause of cancer-related deaths worldwide.[1] In the United States, the incidence of HCC has increased from 4.4 per 100,000 (95% CI, 4.3–4.5) in 2000 to 6.7 per 100,000 (95% CI, 6.6–6.8) in 2012.[2] The curative treatment options of liver transplantation or liver resection are limited to patients who present with early-stage disease, typically defined as Barcelona Clinic Liver Cancer (BCLC) stage A. The treatment of more advanced disease, defined as BCLC stages B and C, has been a challenge; locoregional modalities such as transarterial chemoembolization or radioembolization for patients with BCLC stage B disease result in a median survival of about 20 months[3]; sorafenib, the multitargeted kinase inhibitor, is the only approved systemic therapy for advanced HCC (BCLC stage C) with a median survival of 10.5 months reported in the SHARP trials and 6.5 months in the Asia Pacific study.[4,5] Needless to say, there is a pressing need for more effective treatment options that would result in longer survival and expand the chance of cure to more patients.

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BRIEF OVERVIEW OF THE CURRENT STATUS OF TREATMENT OF ADVANCED HCC

As noted earlier, sorafenib continues to be the only standard therapeutic option for patients with advanced HCC, commonly defined as those with extrahepatic metastases, vascular invasion, or multifocal liver-limited disease that has failed locoregional therapy. Since the approval of sorafenib, there were multiple randomized phase III trials that compared other targeted agents or a combination of targeted agents to sorafenib, all of which failed to reach their primary endpoint (Table 1).[6–10] At the time of this review's publication, a press release had recently reported that a randomized phase III study of lenvatinib versus sorafenib in patients with HCC who had not previously received systemic treatment reached its primary endpoint of noninferiority for overall survival (OS), but with superior response rates and progression-free survival compared with sorafenib. In the setting of second-line treatment (after sorafenib failure), prior to the results of the RESORCE trial, several phase III trials comparing agents such as brivanib,[7] ramucirumab,[11] and everolimus[12] to placebo had failed to show an improvement in OS. In the RESORCE study,[13] patients with documented radiologic progression on sorafenib who had tolerated a dose of 400 mg or higher of sorafenib daily for 20 of the last 28 days, were randomly selected in a 2:1 fashion to receive regorafenib versus placebo. Regorafenib resulted in superior OS (10.6 vs. 7.8 months; HR 0.62, 95% CI, 0.50–0.78) and became the first agent to show a clinically and statistically meaningful benefit after sorafenib failure.

THE RATIONALE FOR IMMUNOTHERAPY IN HCC

Evidence of Antitumor Immunity in Patients With HCC

Despite being rare, there are scattered reports in the literature of spontaneous HCC regression, which has been attributed to the host antitumor immune response as well as vascular events.[14,15] Patients with HCC tumors who have a marked proinflammatory T-cell infiltrate with a high CD4:CD8 ratio have a reduced risk of tumor recurrence following liver transplantation; the hypothesis behind the CD4:CD8 ratio impact is that CD8+ cytotoxic T cells rely on CD4+ helper lymphocytes for maximal effect.[16] Similarly, patients with resected HCC whose tumors contained a low intratumoral T-regulatory lymphocytes (Tregs) level in combination with high intratumoral activated CD8+ cytotoxic T cells (CTLs) had improved disease-free survival and OS.[17] The other evidence of immunogenicity in HCC comes from the presence of tumor-associated antigens recognized by CTLs in 50%–70% of patients with HCC[18,19]; the tumor-associated antigens recognized by CTLs included cyclophilin B, squamous cell carcinoma antigen recognized by T cells (SART) 2, SART3, p53, multidrug resistance-associated protein (MRP) 3, alpha-fetoprotein (AFP), and human telomerase reverse transcription (hTERT). Unfortunately, the presence of intratumoral T-cell infiltration that could inhibit tumor growth and the detectable adaptive immune responses against tumor antigens are counteracted by tolerance-inducing mechanisms that prevent a consistent effective antitumor response.[20]

The Immunosuppressive Environment of HCC

Both the liver itself and the tumor environment possess a diverse armamentarium of mechanisms that suppress antitumor immunity. These mechanisms of immune tolerance have been described in several elegant reviews,[21,22] and a detailed discussion of these mechanisms is beyond the scope of this article. However, we will highlight a few examples of immunosuppressive processes that represent opportunities for potentially effective immunotherapeutic interventions.

Upregulation of inhibitory molecules.—CTLA-4, PD-1, TIM-3, LAG-3 (lymphocyte activation gene 3 protein), and BTLA (B and T lymphocyte attenuator) are coinhibitory molecules known as immune checkpoints that regulate the activation of T cells to prevent unchecked immune activation and collateral tissue damage.[23,24] Lower expression of levels of the PD-1 ligands, PD-L1 and PD-L2 in HCC tumor cells, is associated with superior disease-free survival and OS.[25] CD4 and CD8 lymphocytes infiltrating the tumor in hepatitis B–related HCC show expression of TIM-3 and are replicative senescent.[26] In the setting of hepatitis C infection, there is evidence of apoptosis in immune cells and spontaneous T-cell exhaustion, which are at least partially driven by upregulation of TRAIL, LAG-3, TIM-3, PD-1, and CTLA-4 in hepatitis C–primed peripheral blood mononuclear cells.[27]

Production of immunosuppressive cytokines.—Interleukin-10 (IL-10), TGF-β, IDO, and arginase are among a long list of immunosuppressive molecules that HCC cells can produce to escape innate and adaptive immunity.[22] Tumor-associated macrophages in HCC produce IL-6, which in turn enhances IL-10 production by myeloid-derived suppressor cells (MDSCs); high IL-10 levels downregulate HLA class II expression by macrophages, which impairs antigen presentation, stimulates Treg cell expansion, and blocks natural killer cell activation.[28] IDO inhibits T-cell activation and proliferation, and promotes Treg cell function.[29,30] In the setting of HCC, IFN-γ production suppresses T-cell proliferation and functionality by a mechanism that is blocked upon addition of the IDO inhibitor 1-methyl-tryptophan.[31]

Shift toward an immunosuppressive environment driven by immune cell subtypes.—MDSCs represent a diverse group of myeloid cells that suppress antitumor immunity and produce protumoral effects. Patients with HCC have been shown to have increased levels of CD14+ HLA-DR−/low MDSCs in the peripheral blood and in tumors. These MDSCs are unable to stimulate an allogeneic T-cell response, suppress T-cell proliferation, and induce CD4+ CD25+ Foxp3+ Treg expansion.[32] MDSCs contribute to the immunosuppressive milieu of HCC through a variety of other mechanisms that are detailed in a review by Wan et al.[33] One notable example is the inhibition of natural killer cell cytotoxicity and cytokine release by MDSCs (CD14+ HLA-DR−/low).[34] Tumor-associated macrophages constitute another cell type with protumor effects by inducing angiogenesis and promoting tumor cell invasion and metastasis.[35] There is evidence of active dynamic interaction and communication between MDSCs, Tregs, and tumor-associated macrophages, which creates a network of immunosuppression. On one hand, tumor-associated macrophages produce chemokines such as CCL17, CCL18, and CCL22, which preferentially attract Treg and Th2 cells to the tumor and, in turn, impair CTL activation.[36]

On the other hand, Treg production of IL-10, IL-4, and IL-13 can promote differentiation of monocytes into immunosuppressive tumor-associated macrophages.[37]

Impact of Tumor Immune Milieu on Patient Outcomes in HCC

There is an emerging body of literature linking the status of antitumor immunity to outcomes of patients with HCC treated with various modalities. The prognostic association of various components of the antitumor immunity with survival provides another justification for immunotherapy in this disease. In a study of 36 patients with HCC treated with hepatic intra-arterial infusion, the frequency of MDSCs was significantly lower in the group with complete or partial response to therapy compared with the group with stable disease or progressive disease ($p = .006$); furthermore, the OS of patients with a high frequency of MDSCs before treatment was significantly shorter ($p = .003$). The frequency of MDSCs remained as a prognostic marker on multivariate analysis.[38] Gao and colleagues evaluated the impact PD-L1 and PD-L2 expression in tumors in patients with resected HCC; the median disease-free survival and OS were 14.9 and 29.6 months, respectively, for PD-L1–positive patients compared with not reached and 59.4 months for PD-L–1 negative patients, respectively ($p = .047$ and $p = .029$, respectively). Similarly, there was a significant association between PD-L2 expression and OS ($p = .041$).[39] In another study, CD3+, CD4+, CD8+, Foxp3+, and granzyme B+ tumor-infiltrating lymphocytes were assessed by immunohistochemistry in tissue microarrays containing HCC from 302 patients. The presence of low intratumoral Tregs in combination with high intratumoral activated CD8+ CTLs, a balance toward CTLs, was an independent prognostic factor for both improved disease-free survival ($p = .001$) and OS ($p < .0001$). Five-year OS and disease-free survival rates were only 24.1% and 19.8%, respectively, for the group with intratumoral high Tregs and low activated CTLs, compared with 64.0% and 59.4%, respectively, for the group with intratumoral low Tregs and high activated CTLs, respectively.[17]

CHECKPOINTS AS A THERAPEUTIC TARGET IN THE CLINIC

Targeting CTLA-4

As discussed previously, the upregulation of inhibitory immune checkpoints including CTLA-4 and PD-1 has been reported in the setting of HCC and has been associated with outcome. Given the success of targeting CTLA-4 and PD-1/ PD-L1 in multiple solid tumors, it became important to evaluate the efficacy of checkpoint inhibitors in HCC. Tremelimumab, an IgG2 anti–CTLA-4 monoclonal antibody, was the first checkpoint inhibitor to be evaluated in HCC by Sangro and colleagues.[40] Patients with hepatitis C–related HCC, Child-Pugh A or B, and whose disease was not amenable to curative therapy, percutaneous ablation, or locoregional therapy were enrolled. Notable baseline characteristics included a Child-Pugh B status in 43% of patients, presence of portal vein thrombosis in 29%, and extrahepatic metastases in 10%. Twenty-four percent had received prior sorafenib treatment. In the 20 patients evaluable for safety, the most common treatment-related grade 3 or higher adverse events included AST and ALT elevation in 45% and 25%, respectively, total bilirubin elevation in 10%, neutropenia in 5%, and diarrhea and rash in 5% each. Seventeen patients were evaluable for treatment response; three patients (17.6%) had a confirmed partial response lasting 3.6, 9.2, and 15.8 months. Ten patients

(58.8%) had stable disease. Intent-to-treat median time to progression was 6.48 months (95% CI, 3.95–9.14) and median OS was 8.2 months (95% CI, 4.64–21.34). One of the important conclusions of this small study was the feasibility of administration of an anti–CLTA-4 antibody to patients with HCC in the setting of liver cirrhosis and hepatitis C; the adverse events appeared to be manageable and the elevation of AST and ALT were transient and not associated with overall deterioration of liver function. Another important finding of the study is the documentation of antiviral and antitumor immune responses in patients; there was a statistically significant decrease in hepatitis C viral load in 11 patients at day 120 ($p = .011$) and in six patients at day 210 ($p = .017$) along with a general trend to increased number of virus-specific IFN-c–producing lymphocytes.[40]

Targeting PD-1/PD-L1

Nivolumab, a fully human IgG4 monoclonal antibody against PD-1, has been undergoing evaluation in CheckMate 040, a phase I/II study for patients with advanced HCC. Given hypothetical concerns about the risk of inducing immune-mediated fulminant hepatitis and the overall safety of checkpoint inhibition in the setting of viral hepatitis, the phase I part of the study included a classic 3 + 3 dose escalation in parallel separate cohorts of patients with hepatitis B, hepatitis C, and noninfected patients. There was no maximum tolerated dose despite escalation up to 10 mg/Kg every 2 weeks. One dose-limiting toxicity of grade 2 hepatic decompensation was noted at 10 mg/Kg in the uninfected cohort. The adverse events were consistent with the toxicity profile of nivolumab in other tumor types. During the phase I dose escalation part of the study, grade 3 and 4 treatment-related adverse events occurred in 25% of patients (12 of 48); the most common grade 3 and 4 adverse events were asymptomatic laboratory abnormalities including lipase increase in 13%, AST and ALT increase in 10% and 6%, respectively, and amylase increase in 4%. During the phase II expansion, 214 patients were recruited into one of four parallel cohorts: (1) noninfected sorafenib naive or intolerant, (2) noninfected sorafenib progressors, (3) hepatitis C–infected, and (4) hepatitis B–infected. The safety profile for the phase II expansion was similar to the dose escalation. Baseline characteristics for the overall patient population (dose escalation and expansion combined) were notable for 67% of patients who had prior treatment with sorafenib, 76% with extrahepatic metastases, and 8% with vascular invasion. All patients (except two) had Child-Pugh scores of 5 or 6. In terms of efficacy, the objective response rate based on RECIST 1.1 was 15% (including three complete responses) during dose escalation and 20% during dose expansion. Responses were seen across all cohorts independent of etiology. During dose escalation, for which there was adequate follow-up, the median duration of response was 17 months (95% CI, 6–24) and the median OS was 15 months (95% CI, 9.6–20.2). Median OS in the uninfected sorafenib progressor cohort was 13.2 months (95% CI, 8.6–NE [not estimable]); medians were not reached in the other dose-expansion cohorts. There was no clear association between PD-L1 expression on tumor cells ($< 1\%$ vs. $\geq 1\%$) and the likelihood of radiologic response. Other biomarkers are being evaluated in tumor samples and peripheral blood.[41–43]

In addition to nivolumab, other studies evaluating pembrolizumab, durvalumab and other PD-1– or PD-L1–targeting agents have been ongoing for hepatocellular carcinoma. Ongoing phase III studies are critical to validate the promising signal seen in early-phase trials; such

phase III studies include Keynote-240, comparing pembrolizumab to placebo in patients who had documented disease progression on sorafenib or intolerance to sorafenib (NCT02702401), and CheckMate 459, comparing nivolumab with sorafenib in patients with advanced HCC who had not received other prior systemic therapy (NCT02576509).

Other checkpoints and costimulatory receptors.—As is the case with other tumors, there is a rationale to block other immune checkpoints (such as Lag-3, TIM-3, etc.) and to evaluate antibodies that agonistically bind costimulatory receptors on immune cells (OX40, GITR, CD137). Early-phase studies evaluating such agents are ongoing, and some of them allow patients with HCC. There are also emerging efforts to combine agents that targets immune checkpoints such as PD-1 and CTLA-4 as well as other combinations involving costimulatory receptors.

Other combinations involving immune checkpoint antibodies.—There is a large number of preclinical and clinical studies that are evaluating multiple modalities in combination with immune checkpoint inhibitors; the unifying concept is to harness various components of the immune system or to circumvent potential resistance mechanisms. An extensive review of this field is beyond the scope of this article. However, we will highlight a few approaches that highlight the potential of such combinations. Stereotactic radiation, in which a high dose of radiation is delivered to a limited area, can induce cell death and release of tumor antigens that can be recognized by the immune system to generate a tumor-specific T-cell immune response. In a preclinical model, the administration of an anti–PD-1 antibody concurrently with SBRT resulted in superior survival and was associated with increased CD8+ CTLs in the tumor and increased expression of PD-L1 on tumor-infiltrating macrophages.[44] Studies evaluating the combination of PD-1 or PD-L1 inhibitors with SBRT are recruiting patients with a variety of solid tumors. Embolization and ablative techniques have also been shown to release tumor antigen and stimulate antitumor immunity, which may be further enhanced with the simultaneous administration of checkpoint inhibitors. The combination of the anti–CTLA-4 antibody, tremelimumab, with subtotal radiofrequency ablation or chemoablation was evaluated in 32 patients with HCC; the majority of the patients' disease had progressed on or had been intolerant to sorafenib. This pilot study established the feasibility of the combination, as there were no dose-limiting toxicities and the side effect profile was consistent with that of tremelimumab. Nineteen patients had lesions that were evaluable for response outside of the areas treated with ablation or transarterial chemoembolization; five patients (26%; 95% CI, 9.1%–51.2%) achieved confirmed partial responses. The frequency of activated CD8+ T cells in the peripheral blood was increased by twofold over baseline and was sustained for at least 12 weeks. Tumor biopsies at the time of ablation revealed an increase in tumor-infiltrating lymphocytes compared with baseline.[45] The intriguing clinical and biologic activity noted in this pilot study should be further evaluated in subsequent larger but carefully designed trials.

LEVERAGING THE IMMUNE SYSTEM BEYOND CHECKPOINT INHIBITION

Immunotherapeutic approaches beyond checkpoint inhibition have been evaluated for hepatocellular carcinoma. These include adoptive cellular therapy, vaccines, and oncolytic viruses. Below we will highlight various examples of such approaches in HCC.

Cell Therapy

There are various forms of cell therapy including cytokine-induced killer cells (CIKs), tumor-infiltrating lymphocytes, and genetically modified T cells. Adoptive cell therapy using CIKs has been evaluated in the clinic for HCC. The promise of CIKs is highlighted in the results of a multicenter, open-label, randomized phase III study that evaluated their safety and efficacy as adjuvant therapy after curative therapy for HCC; 230 patients treated by surgical resection, radiofrequency ablation, or percutaneous ethanol injection were randomly assigned to receive immunotherapy (injection of 6.4 109 autologous CIKs, 16 times over 60 weeks) or no adjuvant therapy (control). The autologous CIKs consisted of CD3+/CD56+ T cells, CD3+/CD56– T cells, and CD3–/CD56+ natural killer cells. The median recurrence-free survival (primary endpoint) was 14.0 months longer in the immunotherapy group (44.0 months) than in the control group (30.0 months). The frequency of grade 3 and 4 adverse events and of serious adverse events was comparable between the two groups.[46] The majority of the patients in this study had hepatitis B, tumors that measured less than 3 cm, and were treated with RFA most commonly; the positive results need to be further evaluated in various populations to validate the benefit, which could offer a highly impactful option in an area of unmet need. This study also serves as a good example of the potential role of immunotherapeutic approaches in early stages of HCC, in contrast to the checkpoint inhibitors, which are now being evaluated largely in advanced disease. Another example of the emerging role of cellular therapy in various stages of HCC is highlighted in a meta-analysis of studies that evaluated transarterial chemoembolization with any form of cell therapy including CIKs, tumor-infiltrating lymphocytes, natural killer cells, and dendritic cells. Patients who underwent cell therapy had higher 6-month PFS (OR, 2.78; $p = .05$), 12-month PFS (OR, 3.56; $p < .00001$), 6-month OS (OR, 2.81; $p = .0009$), 12-month OS (OR, 3.05; $p < .00001$), and 24-month OS (OR, 3.52; $p < .0001$).[47]

Oncolytic Virus Therapy

Various viral constructs have been evaluated in HCC preclinical models including adenoviruses, vaccinia viruses, and listeria monocytogenes. The general idea is to use viruses to deliver specific molecules into the liver tumor.[21] JX-594 is an oncolytic and immunotherapeutic vaccinia virus expressing granulocyte-macrophage colony-stimulating factor that has cytoreductive effects and activates both innate and adaptive immune responses.[48,49] Intratumoral injections of JX-594 were shown to be safe with an early signal of efficacy[50]; however, a randomized phase IIB study failed to demonstrate improved OS in patients with advanced HCC whose disease had failed prior first-line chemotherapy, as reported by the company, and did not reach its primary endpoint improvement of OS.[51] An ongoing phase III study is comparing the combination of JX-594 (Pexa-Vec) with sorafenib versus sorafenib alone in first-line treatment of HCC (NCT02562755). In addition, a trial combining JX-594 (Pexa-vec) with anti–PD-1 therapy is pending activation.

THE FUTURE: CHALLENGES AND OPPORTUNITIES

As the body of preclinical and clinical data for immunotherapy in HCC continues to grow, it is critical to focus efforts on identifying biomarkers that would enhance patient selection for the various immune therapeutic modalities and that would allow for smarter combinations

based on potential escape pathways and mechanisms of resistance. Another challenge would be to expand the clinical benefit to various patient subgroups, including those with compromised liver function (beyond Child-Pugh A) as well as patients with early- and intermediate-stage disease. Additional investigations in the area of adjuvant therapy and in combination with standard effective locoregional modalities are needed. Lastly, it is critical to account for the biologic heterogeneity of HCC and carefully evaluate the potential interplay between etiology and the oncogenic pathways in the tumor and the tumor microenvironment. The efficacy of certain immunotherapeutic interventions may vary based on such interplay and should be accounted for. In conclusion, the emerging body of evidence suggests that immunotherapeutic modalities have a real potential of bringing new hope to patients with HCC across all stages and etiologies.

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KEY POINTS

- HCC continues to represent a major therapeutic challenge.
- HCC is an immunogenic disease.
- Antitumor immunity is suppressed by various mechanisms in HCC.
- Checkpoint inhibition has shown consistent and promising early signals of efficacy.
- Combinatorial approaches of various immunotherapies or of immunotherapy with standard modalities hold great promise.

TABLE 1.

The Challenge: First-Line Randomized Phase III Trials

Phase III	Target(s)	Time to Progression (Months)	Overall Survival (Months)
Sunitinib vs. sorafemb (Cheng et al[6])	VEGFRs, PDGFRs, c-kit, (Flt)3, RET	3.8 vs. 4.1; HR 1.13, 95% CI, 0.98–1.31; p = 0.16	7.9 vs. 10.2; two-sided p < .0014
Brivanib vs. sorafenib (Llovet et al[7])	VEGFR2, FGFR	4.2 vs. 4.1; HR 1.01, 95% CI, 0.88–1.16	9.5 vs. 9.9; HR. 1.06, 95% CI, 0.93–1.22; p < .373
Linifanib vs. sorafenib (Cainap et al[8])	VEGFR and PDGFR	5.4 vs. 4; HR 0.76, 95% CI, 0.64–0.89; p < .001	9.1 vs. 9.8; HR 1.04, 95% CI, 0.89–1.22; p = NS
Sorafenib + erlotinib vs. sorafenib + placebo (Zhu et al[9])	VEGFR1/2/3, Ras, Raf, EGFR	3.2 vs. 4; HR 1.13, 95% CI, 0.94–1.36; p = 0.91	9.5 vs. 8.5; 0.92, 95% CI, 0.78–1.1; p = 0.2
Doxorubicin + sorafenib vs. sorarfenib CALGB 80802 (Abou Alfa et al[10])	VEGFR1/2, PDFG, Ras, Raf	3.6 vs. 3.2; HR 0.90, 95% CI, 0.72–1.2	9.3 vs. 10.5; HR 1.06, 95% CI, 0.8–1.4