Immunomodulation in hepatocellular cancer

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Abstract: Hepatocellular carcinoma (HCC) is the fastest growing malignancy in the United States in relation to mortality. HCC relies on a complex immunosuppressive network to modify the host immune system and evade destruction. Intrinsic to the liver's function and anatomy, native hepatic and immune cells produce many inhibitory cytokines that promote tolerogenicity and limit immune response. Since the introduction of sorafenib in 2008, no treatment has been able to demonstrate improved survival in patients with advanced HCC post disease progression treated with sorafenib. More recent studies have shown that sorafenib has an immunomodulatory function in addition to inhibition of multiple tyrosine kinases. Clinical trials have aimed to further enhance this immunomodulatory function with other treatments, most promisingly immune checkpoint inhibitors. Additionally, ongoing studies are using combinatorial approaches with immunomodulatory treatment and liver directed therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation. This article will review recent data describing the immunosuppressive network in HCC, recent results of immunotherapies, and combinatorial approaches to treat advanced HCC.

Keywords: Hepatocellular carcinoma (HCC); sorafenib; immunomodulation; immune checkpoint inhibitor

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Introduction

Hepatocellular carcinoma (HCC) is a life threatening malignancy that has become a global healthcare problem (1). HCC is common in regions where hepatitis B and hepatitis C infection are endemic. Alcoholic cirrhosis, diabetes mellitus, obesity, and nonalcoholic steatohepatitis (NASH) are also known risk factors for the development of HCC (2). HCC lethality is multifactorial; several factors are advanced stage at diagnosis, poor residual liver reserve, high rate of recurrence after curative therapies and resistance to chemotherapy. Historically in the United States, HCC is a rare cancer, however its incidence has begun to rise. This may be related to the growing number of hepatitis C carriers and rising frequency of metabolic syndrome. The incidence of HCC has almost tripled since the early 1980s, and it is currently the fastest rising cause of cancer-related deaths in the United States (3,4).

The treatment of HCC is multidisciplinary, involving surgical resection, locoregional therapies, and systemic treatment. For patients with advanced HCC, systemic treatment is the only available option. However, majority of patients unfortunately present with advanced disease with severe liver dysfunction and a poor performance status. Systemic chemotherapeutics are often poorly tolerated with adverse health effects. Particularly, patients with advanced HCC and liver cirrhosis have been shown to have no survival benefit following traditional cytotoxic chemotherapy with poor tolerance (5). Many patients with HCC at the time of diagnosis also have chronic hepatitis

infection. Intensive chemotherapy with immunosuppression increases the risk of reactivating a dormant hepatitis infection leading to treatment complications (6). Due to these comorbidities there has been no established chemotherapeutic regimen approved for the treatment of HCC (7). Systemic therapy is therefore limited to sorafenib for the treatment of advanced HCC (8).

Immunosuppressive networks in HCC

Tumor associated antigens (TAAs) are presented on MHC molecules and induce an inflammatory immune response. TAAs include alpha-fetoprotein (AFP), glypican-3 (GPC-3), and cancer/testis proteins (9,10). In addition to TAAs, neo-antigens arising from specific gene mutations can also elicit anti-tumor immune responses. Stimulatory and inhibitory signals orchestrate the optimal activation and maintenance of the immune system. For the priming and activation of effector T-cells (Teffs), the specific interaction of T-cell receptors and TAAs on the MHC molecules, as well as co-stimulation via ligand/receptor complexes between antigen presenting cells (CD28, CD137, and CD27) and T cells (CD80 and CD86, CD137L, and CD70) are required. Immune checkpoint inhibition is the main signaling pathway preventing over-activation of the immune system when immune cells are chronically exposed to infection or malignancy. Tumor cells are able to modulate the immune checkpoint pathway, allowing them to go undetected by the native immune system. Several key molecules of immune checkpoints have been identified, including cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), T cell membrane protein 3 (TIM-3), killer cell immunoglobulin-like receptors (KIR), and lymphocyte-activation gene 3 (LAG-3) (11).

HCC evades the anti-tumor immunity by creating a complex immunosuppressive network. HCC cells interact with immune and stromal cells through the secretion of immunosuppressive cytokines (9). HCC derived cytokines are able to reduce immune responses as well as modulates its own growth. Through the EGFR ligand, marrow-derived mesenchymal stem cells promote tumor angiogenesis and fibrogenesis. Complimentary growth factor pathways including transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) further mediate this response, also enable unregulated tumor growth.

The liver has tolerogenicity, which is believed to be intrinsic to its anatomy and function. As the major route for processing absorbed nutrients and molecules from the gastrointestinal tract, the liver has adapted to minimize its immune response to intestinal bacteria or pathogen-derived molecules (12,13). Cells native to the liver including hepatocytes, liver sinusoidal endothelial cells (LSECs), Kupffer cells, and liver dendritic cells contribute to tolerogenicity by inducing an anergic phenotype in cytotoxic CD8+ T cells (14-16). Under chronic inflammation from HBV or HCV infection, tumor-infiltrating lymphocytes, Kupffer cells or LSECs have an elevated level of PD-1, CTLA-4, and TIM-3 (17-21), leading to immune system exhaustion. Liver dendritic cells are also less immunogenic than those in other organs and have a reduced role as antigen presenting cells (22). Tumor cells secrete immunosuppressive cytokines including IL-8 and IL-10, which directly suppress cytotoxic T-cells and NK cells (23-26). IL-10 is also a known activator of tumor-associated macrophages (TAMs) via the M2 macrophage polarization pathway, and TAMs are known to promote tumor progression and are associated with a poor prognosis (26). Chronic inflammation of HBV and HCV leads to an even further increase in immunosuppressive cytokines including IL-4, IL-5, IL-8, IL-10, and TGF-β (27,28). This interplay of dysregulation of cytokines and upregulation of immune checkpoint-associated molecules in the liver signifies the exhaustion of Teffs and cytotoxic CD8+ T cells (29). The liver's immune environment in combination with HCC's immunosuppressive nature is a formidable barrier in the treatment of HCC.

Immunomodulation in HCC

Sorafenib

Sorafenib inhibits tumor-cell proliferation and angiogenesis by blocking both the intracellular Raf kinase pathway and extracellular VEGFRs and PDGFR-β associated kinases. Sorafenib improves survival in patients with advanced HCC (8,30). Patients with HCC and liver cirrhosis were able to tolerate sorafenib with a minimal side effect profile HCC (31). Sorafenib has also been reported to have immunomodulatory effects in addition to enhancing the tyrosine kinase inhibition of cancer proliferation and angiogenesis (32,33). Two studies have shown that sorafenib modulates the tumor microenvironment in a murine mouse model (34,35). In the microenvironment of human HCC, sorafenib enhanced antitumor immunity by relieving

intrinsic inhibitions of Teffs (36), modulating dendritic cells (37) and natural killer cells (38). Sorafenib was shown to improve immune responsiveness by increasing the ratio of Teffs to regulatory T cells (Tregs) (39), resulting in reduced expression of immunosuppressive cytokines and growth factors. Sorafenib also enhanced migration of cytotoxic CD8+ T cells and suppressed infiltration of myeloid derived suppressive cells (MDSCs) and Tregs to the liver (32).

Our group demonstrated for the first time that the ratio of CD4+CD127+PD-1– Teffs to CD4+Foxp3+PD-1+ Tregs was significantly increased following treatment with sorafenib in patients with advanced HCC (40). In an *in vitro* experiment with unsorted T cells, there was a marked reduction in the frequency of CD4+CD127+PD-1+ T cells, whereas the frequency of CD4+CD127+PD-1– T cells was enhanced by sorafenib treatment. Sorafenib also decreased the levels of immunosuppressive cytokines IL-10 and TGF-β1, thereby reducing fibrogenesis and the remodeling of the HCC tumor microenvironment. This study suggests that sorafenib has a direct immunomodulatory effect on lymphocytes, as well as indirect effect on the HCC tumor microenvironment helping to reduce the immunosuppressive network in HCC.

The direct immunomodulatory effects of sorafenib in addition to its tyrosine kinase inhibition suggest that it could be an adjunct in combination with other immunotherapeutic approaches (40,41).

Immune checkpoint inhibitor

Checkpoint inhibitors have significantly expanded the treatment options in a number of solid and hematologic malignancies. Although there are many potential immune checkpoints, CTLA-4 and PD-1 are two main immune checkpoints that have been extensively studied with targeted therapies. CTLA-4 and PD-1 systems help prevent overstimulation of immune responses to both foreign and self-antigens (42-44). CTLA-4 expression is regulated by negative feedback. Increasing activation of T-cell receptors and proinflammatory cytokines results in increased CTLA-4 expression and a muted immune response. PD-1 is a surface molecule expressed on many immune cells including T cells and B cells. Ligands of PD-1 (PD-L1 and PD-L2) are expressed on various tissues including cancer cell surfaces. The specific binding of PD-1 and PD-L1 or PD-L2 leads to immune system exhaustion and upregulation of Tregs (45). As in CTLA-4 expression, the expression of PD-1 and PD-L1 and 2 is also increased by the degree of pro-inflammatory cytokines (46,47). Many side effects from immune checkpoint inhibitors have been reported, but these side effects are often mitigated by anti-inflammatory medications such as glucocorticoids (48-50). Secondary to their immunomodulatory nature, this drug class has been approved for a wide variety of malignancies.

Despite their use in a large number of conditions, few clinical trials have studied the use of checkpoint inhibitors for patients with hepatocellular carcinoma. Sangro *et al.* (51), performed a phase I clinical trial and reported that tremelimumab, an anti-CTLA-4 antibody showed a partial response rate of 17.6% and disease control rate of 76.4%. Sangro *et al.* also showed a significant decrease in hepatitis C viral load in patients with inoperable hepatocellular carcinoma and chronic hepatitis C infection. A preliminary report of CheckMate 040 (Phase I/II trial for patients having advanced HCC, including those with hepatitis C virus (HCV), hepatitis B virus (HBV), and uninfected patients) was presented by El-Khoueiry *et al.* in 2015. It demonstrating that, among 39 patients with advanced hepatocellular carcinoma, 5% and 18% of patients showed complete and partial responses, and overall survival at 6 months was 72% (52). Another preliminary result from CheckMate 040 was reported in January 2017 at the Gastrointestinal Cancers Symposium, American Society of Clinical Oncology (53). Out of 37 patients in the escalation cohort and 145 patients in the expansion cohort, the objective response rates were 16.2% and 18.6%, with a median overall survival of 15.0 and 13.2 months, respectively. PD-L1 expression did not correlate with the response rate to nivolumab. Currently, CheckMate 459 is recruiting patients with advanced hepatocellular carcinoma, comparing nivolumab to sorafenib as a primary treatment (54). These reports on immune-checkpoint inhibitors for patients with advanced hepatocellular carcinoma suggest that nivolumab is well tolerated without many of the side effects reported in patients treated for other malignancies. Nivolumab also had a durable response in patients irrespective of hepatitis B or C viral status comparing nivolumab to sorafenib as a primary treatment (55). Our group will begin a phase II clinical trial with pembrolizumab and sorafenib for patients with advanced HCC in 2017. *Table 1* shows clinical trials currently available with checkpoint inhibitors in patients with hepatocellular carcinoma.

Table 1 Clinical trials currently available with immune checkpoint inhibitors in HCC

ClinicalTrials.gov identifier	Agent(s)	Target	Locoregional therapy	Study design	First or second line
NCT02795429	PDR001/INC280	PD-1/cMET	None	Ib/II	Second line
NCT02702401	Pembrolizumab	PD-1	None	III	Second line
NCT02702414	Pembrolizumab	PD-1	None	II	Second line
NCT02856425	Pembrolizumab/ Nintedanib	PD-1/VEGFR, PDGFR, FGFR	None	I	Second line
NCT02821754	Tremelimumab/ Durvalumab	CTLA-4/PD-L1	RFA/TACE/Cryoablation	Pilot	Second line
NCT02988440	PDR001/ Sorafenib	PD-1/Raf, VEGFR, PDGFR	None	Ib	First line
NCT02989922	SHR-1210	PD-1	None	II/III	Second line
NCT02576509	Nivolumab/ Sorafenib	PD-1/Raf, VEGFR, PDGFR	None	III	First line
NCT03033446	Nivolumab	PD-1	Radioembolization	II	First line
NCT02859324	CC-122/Nivolumab	CRBN/PD-1	None	I/II	Second line
NCT02423343	Galunisertib/ Nivolumab	TGF-β1/PD-1	None	Ib/II	Second line
NCT01658878	Nivolumab/ Ipilimumab	PD-1/CTLA-4	None	I/II	First and second line
NCT02837029	Nivolumab	PD-1	Yttrium microspheres	I/Ib	First and second line
NCT01853618	Tremelimumab	CTLA-4	RFA/TACE/SBRT/ Cryoablation	Pilot	Second line

HCC, hepatocellular carcinoma; PD-1, programmed death 1; CTLA-4, cytotoxic T lymphocyte associated protein 4; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; TGF-β, transforming growth factor β; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy.

Tumor ablation and embolization

Locoregional therapies remain a standard of care in HCC although these therapies are not curative for patient with the Barcelona Clinic Liver Cancer (BCLC) intermediate stage (B). Previously, tumor ablation or embolization were considered to locally destroy HCC tumors and slow tumor progression. However, many recent studies have shown that it can also stimulate or modulate tumor immunity.

Radiofrequency ablation (RFA) and microwave ablation (MWA) are the two most common ways to deliver both targeted and large amounts of energy to a tumor. Both of these methods directly induce tumor necrosis by supplying high temperatures and energy. Tumor destruction leads to the release of intracellular components including heat shock proteins, which are highly immunogenic (56). This activates antigen-presenting cells and enhances local tumor immunity (57). Studies have also shown that MWA and RFA change the level of cytokine levels that are directly associated with tumor immunity (58). Patients with higher levels of heat shock proteins in the peripheral blood after treatment have been shown to have improved survival (59,60), and it supports the immunomodulatory effect of RFA and MWA. Ito *et al.* (61), demonstrated that RFA was significantly immunogenic in a preclinical mouse model when performed prior to surgical resection (pre-resectional RFA). RFA caused a marked increase in antigen-specific CD8+ T cells within the tumor microenvironment and tumor-draining lymph node. It also delayed growth of distant tumors through systemic CD8+ T cell-mediated antitumor immunity.

Other studies have shown that cryoablation can also induce immune-mediated alteration of tumor immunity. While RFA and MWA induce immunogenicity by destroying tumors and releasing cellular debris, cryoablation causes cellular inflammation through low temperatures and freezing tumor cells (62,63). Unlike high energy ablation, cellular components in frozen cells are not destroyed. These intact cellular components, when released, can elicit an immune response (64,65) similar to the necrotic debris in RFA and MWA.

Transarterial chemoembolization (TACE) is used for HCC patients with unresectable, encapsulated tumors, and preserved liver function (66,67). TACE also has a potentially immunomodulatory effect similar to RFA or MWA. TACE has been shown to increase peripheral circulation of T helper 17 cells, a pro-inflammatory T cell (68,69), and a markedly decrease in CD4+CD25+ Tregs, an anti-inflammatory cell (70). TACE also altered the cytokine profiles (71), the level of T cell activation, and subpopulations of immune cells (72).

Immunomodulatory effects of tumor embolization and radiation therapy are thus opening up the possibility that such non-surgical treatment may be combined with immunotherapies.

Future perspectives

Combinatorial approaches

Hepatocellular carcinoma has a complex immunosuppressive network as discussed above. HCC is also a heterogeneous tumor with an often unpredictable and inconsistent response to treatment. Within a tumor nodule, HCC cells share a common mutation driving carcinogenesis (driver mutation) with other passenger mutations with unknown roles in carcinogenesis and progression. In addition, cells native to the liver contribute to tolerogenicity given its intrinsic anatomy and function. Sorafenib, which is immunomodulatory, is not curative, and therefore, patients treated with sorafenib have eventual disease progression. This unsatisfactory response to sorafenib monotherapy in the context of heterogeneous and immunosuppressive tumor environment suggests combinatorial approaches of immunomodulation.

As demonstrated by Kalathil *et al.*, the combined depletion of Tregs, MDSC, and PD-1+ T cells from patients with HCC resulted in augmentation of CD8+ T-cell granzyme B production and an increase in the number of CD4+ T cells that produce IFN-γ (73). This data suggests that combination approaches may better enhance endogenous antitumor responses compared to monotherapies. With this evidence, many combinatorial approaches to treat HCC with locoregional and systemic immunosuppression have been attempted. However, one of the most important issues of combinatorial therapies is that most HCC patients have underlying liver cirrhosis. The combination of medications or methodologies could increase liver toxicity resulting in adverse outcomes. In the clinical setting it is crucial to ensure a safe liver toxicity profile when using combinatorial treatment approaches.

Liver directed therapies including local tumor ablation have been widely used for advanced HCC, and these are now known to be immunomodulatory as mentioned above. Through ablation mediated tumor destruction cellular debris can enhance tumor-specific locoregional antigen presentation (13). When combined with immune checkpoint inhibitors, the ablative therapies have the potential of having a synergistic immunomodulatory effect. Studies have aimed to quantitate the role of these liver directed therapies when combined with sorafenib or immune checkpoint inhibitors. In a pilot study, a CTLA-4 inhibitor, tremelimumab in combination with subtotal TACE or RFA in patients with advanced HCC was safe and feasible (74). One current study is investigating durvalumab (PD-1 inhibitor) and tremelimumab combined with ablation therapies including RFA, TACE, or cryoablation for patients with advanced liver or biliary tract cancer (NCT02821754). A similar study enrolls patients with HCC for treatment with tremelimumab and chemoembolization or ablation (NCT01853618). Another clinical trial aims at assessing the synergistic immunomodulatory effect of TACE and autologous immune cell therapy in HCC (NCT01828762).

Sorafenib has also been combined with tumor embolization or ablation to assess the joint immune modulating response. There are a number of clinical trials underway including NCT00919009, NCT01556815, NCT01319942, NCT00768937, NCT01605734, NCT02529761, NCT02504983, and NCT01906216. Clinical trials on the combination of sorafenib and immunotherapy are underway: sorafenib and vaccinia virus-based immunotherapy are combined (NCT02562755); and anti-PD-1 antibody, PDR001 is in combination with sorafenib (NCT02988440).

Hepatitis viral infection and HCC treatment

Patients with chronic HBV, HCV, human immunodeficiency virus (HIV), or tuberculosis have constant exposure to viral or bacterial antigens. As a consequence, the expression of PD-1, PD-L1, and PD-L2 is upregulated, and the T cell- or NK cell-mediated antiviral or antibacterial immune response is attenuated (75). In patients with chronic HBV, PD-1+ T-cells are impaired in their antiviral effector functions (76,77). Clinical studies have aimed to assess the response of HBV, HCV, and other chronic infections to immune checkpoint inhibitors, with a goal of reversing T-cell exhaustion. One such study has shown that the inhibition of PD-1 resulted in increased production of proinflammatory cytokines including IFN-γ and IL-2 in patients with chronic HBV (78). Another study showed that patients with chronic HCV had a significant decrease in the HCV viral load when they received nivolumab (79).

It is important to monitor the differential responses to immune checkpoint inhibitors for patients with HBV or HCV as well as non-infected patients with HCC, due to a risk of viral reactivation. As mentioned above, a preliminary report of CheckMate 040 (52) showed that nivolumab was well tolerated with a durable response in patients with HCC infected with HBV and HCV with no evidence of viral flare. However, recent reports have demonstrated an unexpectedly high rate of the recurrence of hepatocellular carcinoma post-treatment when hepatitis C viral treatment rapidly decreased hepatitis C viral load. It is suspected that the disruption or dysregulation of immune surveillance upon a rapid decrease in hepatitis C viral load may trigger the emergence of metastatic clones (80-83). While some studies suggest that the better control of HCV reduces the incidence of HCC, other studies suggest that the incidence of HCC increases when HCV is treated and controlled with antiviral regimens (83-85). These contradictory results seem to be associated with the complex intertwining of hepatitis virus, cirrhosis, and HCC, as well as various factors such as the degree of cirrhosis compensation, portal hypertension, and the immunosuppressive tumor microenvironment (83,84,86). Without further investigation, no clear immune system relation can be elucidated between hepatitis viral infection and HCC. Despite local and systemic complexity of the immune system in HCC with hepatitis viral infection, there is limited data about the interaction of hepatitis virus with immune checkpoint inhibitors. Therefore, when hepatitis virus-infected patients with HCC are treated with immunomodulators, it is mandatory to closely monitor the safety profile and hepatitis viral loads. It is expected that there will be more research and clinical studies on the interplay of hepatocellular carcinoma and hepatitis viral infection.

Chimeric antigen receptor T cell

The chimeric antigen receptor (CAR)-T cell is an engineered tumor-targeted T cell created through the genetic transfer of tumor antigen specific receptors. The three main elements of CAR-T cells are an extracellular antigen binding domain, a transmembrane domain, and a cytoplasmic signaling domain (87). Third generation CAR-T cells utilize at least two cytoplasmic signaling domains to promote the proliferation of CAR-T cells and anti-tumor activity (88-90). In hematologic malignancies, particularly acute lymphocytic leukemia, CAR-T cell therapy has been widely used and has shown promising results.

CAR-T cells have also been used for patients with solid cancers including ovarian cancer (91), renal cell carcinoma (92), and breast cancer (93) although there have been on-going tolerance and safety issues. Early stage clinical trials are underway for patients with HCC, but clinical data on the response rate or safety profiles have not been reported. Several clinical trials with CAR-T cells targeting different antigens are underway: mucin-1 (NCT02587689), epithelial cell adhesion molecule (EpCAM) (NCT02729493), CD133 (NCT02541370), and glypican-3 (NCT02395250, NCT02723942, and NCT02715362).

Cytokine related therapy

As discussed above, one of the main components of the immunosuppressive network in HCC is the disarray of cytokines. Several therapies have aimed to modify the cytokine environment for the treatment of HCC. In addition, there have been multiple clinical trials utilizing cytokine-induced killer cells (CIKs) (94,95). CIKs are autologous peripheral mononuclear cells created *ex vivo* by incubation with cytokines including IFN-γ, IL-1, IL-2, and anti-CD3 antibody. These cells bypass immune priming and T-cell activation and are able to directly target malignant cells. Ma *et al.* analyzed previously published data on CIKs therapy and demonstrated that CIKs therapy improved overall survival, progression free survival, overall response rate, and quality of life (95). However, a phase

III study with 200 patients randomized to adjuvant CIKs or placebo demonstrated a prolonged time-to-recurrence without improvement of disease free survival or overall survival (96). There are ongoing clinical trials to assess CIKs therapy (NCT02851784, and other completed trials). Secondary to its immunomodulatory design, clinical trials have used combinatorial approaches with CIKs and anti-PD-1 therapy (NCT02886897), as well as CKIs and MWA (NCT02851784). Clinical trials with other systemic immunomodulators and CIKs are expected.

TGF-β is one of the main cytokines associated with fibrogenesis and angiogenesis. However, evidence suggests that its role is primarily as an immunosuppressive cytokine by modulating Treg cells (97). Its role in enhancing Treg activity suggests that TGF-β is one of the main components of the immunosuppressive network in HCC. One study presented at the ASCO annual meeting in 2014 provided promising evidence about TGF-β1 inhibitor in patients with advanced HCC (98). There are ongoing clinical trials, including galunisertib, a TGF-β1 inhibitor in combination with sorafenib or ramucirumab (NCT02240433, NCT01246986, and NCT02178358), nivolumab (NCT02423343), or stereotactic body radiotherapy (NCT02906397).

Oncolytic virus-based therapy

Oncolytic viruses are therapeutic viruses engineered to have cancer specific targets and replicate in cancer cells. Transthyretin-promoter-driven adenovirus (99), AFP-promoter-driven adenovirus (100), membrane metalloproteinase-activated measles virus fusion protein (101), or miR-122-regulated adenovirus (102), as well as JX-594, dl1520, H101 and VSV-hIFN-β have been used in HCC (103). In particular, JX-594 (pexastimogene devacirepvec), a modified Copenhagen strain vaccinia poxvirus has been extensively studied and showed a promising response in patients with HCC (104). Since the first clinical trial (NCT00554372), multiple trials have been completed with anticipated results (NCT01171651, NCT01636284, NCT01387555, and NCT00629759). Oncolytic viruses not only directly destroy cancer cells, but they also elicit an anti-cancer immune response acting as an immunomodulatory agent (103,105). Currently, a clinical trial (NCT02562755) is recruiting patients to compare JX-594-based immunotherapy plus sorafenib compared to sorafenib alone. Subsequent clinical trials combining oncolytic-virus-based immunotherapy with other immunomodulators are anticipated.

Biomarkers and mutational profiles of HCC

The extent to which a cancer with a certain mutational profile or PD-L1 expression responds to immunotherapy is debatable. Many ongoing research projects are utilizing genomic sequencing to better quantify responses to immunomodulators. Studies have shown that stage IV squamous cell lung cancer has a better response to nivolumab than docetaxel regardless of PD-L1 expression levels (106). However, in patients with lung adenocarcinoma and negative PD-L1 levels, survival was similar between docetaxel and nivolumab (107). JAK1/2 mutations have been shown to prevent reactive PD-L1 expression, and patients harboring such tumors would be unlikely to respond to PD-1 blockade therapy (108). In colorectal cancer, patients with mismatch repair mutations have an enhanced response to PD-1 blockade. More specifically, those with high somatic mutation loads are associated with prolonged progression-free survival with pembrolizumab (109). However, there is no known data about the response rate to PD-1 inhibitors with respect to the mutational profile or PD-L1 level in HCC. HCC is a heterogeneous tumor, and the expression of PD-L1 is multifactorial, depending on the stage of tumor, prior treatment regimens, and tumor burden. As discussed above, the microenvironment of HCC involves a complex network of immune cells and liver native cells, as well as multiple pro- or anti-inflammatory cytokines. Therefore, the PD-L1 expression level on HCC tumor needs to be assessed along with these factors for clinical trial enrollment (13,110).

Conclusions

Hepatocellular carcinoma is a chemorefractory malignancy and challenging to treat. The treatment of choice for early stage HCC is surgery or locoregional therapies. Sorafenib is the only FDA-approved medication for advanced HCC, with proven immunomodulatory effects. Recent studies have demonstrated that HCC has a complex immunosuppressive network and tumor microenvironment. Therefore, immunomodulation in HCC has become a main focus of treatment. Early phase trials with monotherapy of an immune checkpoint inhibitor or in combination with other treatment modalities have shown promise across etiologies, and multiple clinical trials are now in progress. In secondary prevention and adjuvant setting, only antiviral

therapy has been successful; the role of immunomodulation needs further investigation. Combinatorial approaches and optimal sequencing to target the heterogeneous, immunosuppressive tumor are expected to be the main avenue of future HCC treatment in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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