

Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: Opportunities and Challenges

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immune checkpoint inhibitors • Hepatocellular carcinoma • Combinatorial immunotherapy strategies • Underlying liver disease • Hepatitis B virus

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common malignancy worldwide, and is especially common in China. A total of 70%–80% of patients are diagnosed at an advanced stage and can receive only palliative care. Sorafenib has been the standard of care for a decade, and promising results for regorafenib as a second-line and lenvatinib as a first-line treatment were reported only 1 or 2 years ago. FOLFOX4 was recently recommended as a clinical practice guideline by the China Food and Drug Administration. All approved systemic therapies remain unsatisfactory, with limited objective response rates and poor overall survival. Immune checkpoint inhibitors (CPIs) offer great promise in the treatment of a rapidly expanding spectrum of solid tumors. Immune checkpoint molecules are involved in almost the whole

process of viral-related hepatitis with cirrhosis and HCC and in the most important resistance mechanism of sorafenib. The approval of nivolumab by the U.S. Food and Drug Administration on September 23, 2017, for the treatment of patients with HCC, based only on a phase I/II clinical trial, is a strong hint that immunotherapy will introduce a new era of HCC therapy. CPI-based strategies will soon be a main approach in anticancer treatment for HCC, and we will observe the rapid advances in the therapeutic use of CPIs, even in an adjuvant setting, with great interest. How shall we face the opportunities and challenges? Can we dramatically improve the prognosis of patients with HCC? This review may provide some informed guidance. *The Oncologist* 2019;24(Special Issue):S3–S10

Implications for Practice: Immune checkpoint molecules are involved in almost the whole process of viral-related hepatitis with cirrhosis and hepatocellular carcinoma (HCC) and in the most important resistance mechanism of sorafenib. As all approved systemic therapies in HCC remain unsatisfactory, checkpoint inhibitor (CPI)-based strategies will soon be a main approach in anticancer treatment for advanced stage of HCC, even in an adjuvant setting. In virus-related HCC, especially hepatitis B virus-related HCC, whether CPIs can control virus relapse should be further investigated. Combination strategies involving conventional therapies and immunotherapies are needed to increase clinical benefit and minimize adverse toxicities with regard to the underlying liver disease.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with more than half the new cases and deaths every year occurring in China [1]. Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, autoimmune hepatitis, alcohol abuse, nonalcoholic steatohepatitis, and several metabolic diseases are among the known risk factors, but the etiologies vary markedly between the Asia-Pacific region and the Euro-American area. The prognosis of patients with HCC at very early or early stages has improved

because of advances in diagnosis and treatment modalities. Unfortunately, 70%–80% of patients cannot benefit from such opportunities because they are diagnosed at an advanced stage, and sorafenib has been the only systemic therapeutic agent available. During the last decade, more than ten drugs have failed to meet clinical endpoints in phase III trials [2]. Numerous genetic pathways in HCC have been studied along with drugs, but thus far, drugs targeting cell proliferation, metastasis, angiogenesis, and metabolite use

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have been studied with minimal success, and in particular, no etiology-specific therapies have been initiated [3–5]. Promising results of global phase III studies including regorafenib as a second-line and lenvatinib as a first-line treatment were reported in 2016 and 2017, indicating the arrival of a new era of HCC target therapy [6], but the improvement in the overall survival (OS) rate remained unsatisfactory.

During recent years, new immune-modulatory agents were introduced for oncological treatment, eventually leading to the clinical breakthrough of checkpoint inhibitors (CPIs) targeting programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T lymphocyte antigen-4 (CTLA-4) [7–10]. Under physiological conditions, these molecules resolve T-cell activation to maintain inflammatory homeostasis, protect tissue integrity, and prevent unwanted autoimmunity [11]. The administration of CPIs in patients with tumors, however, unleashes tumor-directed cytotoxic T cells specific against an unknown spectrum of tumor-associated antigens. This treatment results in a robust multi-targeted immune response that can even induce lasting oncological remission in some patients. The expectations are high that these novel drugs may contribute to the need to develop more effective treatments for HCC. In this review, we will focus mainly on the opportunities and challenges of current CPIs in HCC, especially HBV-related HCC.

IMMUNE CHECKPOINT LEVELS ACCORDING TO CLINICAL DISEASES OF CHRONIC HBV INFECTION

HBV infection is a major public health problem. Approximately 2 billion people worldwide have been infected with HBV, and among them, nearly 250 million people are chronically infected with the virus [12]. Chronic HBV infection manifests heterogeneous clinical outcomes, ranging from asymptomatic chronic HBV carrier status, chronic hepatitis, and cirrhosis to HCC [13, 14]. Chronic HBV infection may be divided into five phases according to the natural history of the infection, namely, the immune-tolerant phase, immune-reactive phase, low replicative phase, reactivation phase, and HBsAg-negative phase. The virological, biochemical, and pathological profiles and associated liver diseases in each phase may vary greatly and manifest differently [15].

Immune dysregulation regulates almost the whole process of HBV-associated liver diseases including HCC, especially with T-cell dysfunction in patients overexpressing PD-1 and CTLA-4 [16–18]. The phenomenon that PD-1 and CTLA-4 are up- or downregulated along with virus relapse or recovery indicates that they have protective effects that involve suppressing cytotoxic T cells, which induce the harmful destruction of infected hepatocytes in self-limited viral hepatitis. In chronic viral hepatitis, the extended upregulation of PD-1 and CTLA-4 is associated with T-cell exhaustion and persistent viral infection, suggesting positive correlations between the expression of immune inhibitory factors and the chronicity of viral disease. Li et al. [19] reported recently that the soluble PD-1 level in HBV-related HCC was significantly higher than in other clinical diseases.

Current antiviral therapeutic agents are highly effective at blocking viral replication, but the discontinuation of therapy prior to the loss of HBsAg generally leads to relapse. New approaches that target host factors, such as

immune checkpoint pathway inhibition, hold promise [20]. In HBV-related HCC, CPIs may benefit both on virus relapse and tumor progression.

PD-L1 PREDICTS POOR PROGNOSIS IN PATIENTS WITH HCC

Because the correlation of CPI response rates with PD-L1 expression levels has been confirmed in various types of cancers [21], whether PD-L1 expression correlates with HCC pathology and patient prognosis has also been examined [22–24]. Although the results obtained were controversial, the first meta-analysis performed by Gu et al. [25] concluded that higher PD-L1 levels predict poor differentiation, higher levels of α -fetoprotein, vascular invasion, and poorer survival [26].

PD-L1 expression in peritumoral hepatocytes is also an independent prognostic factor for OS and disease-free survival (DFS). Dai et al. [27] suggested that future anticancer therapy should target not only residual tumor cells but also the “soil” promoting tumor growth. The levels of circulating PD-L1 might also be of prognostic value in patients with HCC. Finkelmeier et al. [28] performed a prospective cohort study to investigate the relation between soluble PD-L1 levels and the stage of liver disease and HCC. The study concluded that a high soluble PD-L1 level is a possible prognostic indicator for a poor outcome.

Overall, PD-L1 expression in tumor cells is correlated with poorer survival, with peritumoral hepatocytes, and with circulation levels and could be a good target for the treatment of advanced stages of HCC, even in an adjuvant setting after hepatectomy.

PD-L1 EXPRESSION IN ACQUIRED RESISTANCE TO SORAFENIB

Sorafenib has been approved for the treatment of advanced-stage HCC since 2007. It can block the Ras, VEGFR, PDGFR, FLT3, and KIT kinases, increasing the rate of apoptosis and inhibiting cell proliferation, migration, and tumor angiogenesis [29]. However, the reported response rates of sorafenib in current clinical trials have been limited, ranging from 2.3%~9.2%. Identifying the existence of primary or secondary sorafenib resistance mechanisms in HCC is an urgent problem. Recently, some studies have reported novel molecular mechanisms in HCC cells [30–32], and whether PD-L1 expression plays a key role in sorafenib resistance is now under wide investigation.

Liu et al. [33] reported that PD-L1 and DNA methyltransferases (DNMTs) contribute to sorafenib resistance. By inducing sorafenib-resistant HCC cell lines, they found that highly upregulated DNMT1 was positively correlated with PD-L1 overexpression in sorafenib-resistant HCC cells. Chen et al. [34] revealed that pERK-negative, PD-1-positive patients have poorer OS and DFS than pERK-positive, PD-1-negative patients. Accordingly, patients with pERK-positive, PD-1-positive HCC, a minor population (less than 10%) but the one with the worst postoperative recurrence, might benefit the most from combination therapy with anti-PD-1 antibody and sorafenib. Most tumors are pERK negative and PD-1 positive, thus not expected to respond well to sorafenib, and can be subjected to anti-PD-1 immunotherapy alone.

Despite the various etiologies, chronic liver inflammation with cirrhosis and immune cell infiltration resulting from viral infection continue to be important risk factors of HCC [35]. Although HCCs are highly vascularized tumors, their growth often outpaces the necessary blood supply, leading to hypoxia in the tumor and the adjunct tissue; meanwhile, sorafenib administration deteriorates the hypoxic microenvironment and leads to the upregulation of PD-L1 and CXCL12, which belongs to the CXC chemokine family and has a vital impact on immune cell migration and metastasis [36]. The recruitment of immunosuppressive cells partly mediated by hypoxia-induced upregulation of CXCR4 and its endogenous ligand CXCL12 in HCC was observed in a mouse model. Additionally, in an orthotopic model, the combination of PD-1 inhibitors, CXCR4 inhibitors, and sorafenib had an antitumor effect [37]. Hypothetically, combining CXCR4 inhibitors with CPIs in patients with HCC would be a rationale treatment approach.

CPI MONOTHERAPY IN HCC

Nivolumab

“Nivolumab makes headwinds into HCC,” Wayne Kuznar [38] announced in August 2015, pointing to the first report of the use of PD-1 inhibitor in patients with advanced HCC, presented by El-Khoueiry at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2015. Since the CheckMate 040 trial [39] began, nivolumab has been approved in the U.S. and the European Union for the treatment of melanoma, refractory non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), Hodgkin’s disease, and squamous cell carcinoma of the head and neck, as well as for urothelial carcinoma only in the U.S. Nivolumab monotherapy in cases of these approved indications can improve the OS or provide clinical benefit.

The CheckMate 040 trial was a prospective, noncomparative, phase I/II dose study of nivolumab that assessed its safety and clinical benefit across multiple HCC etiologies, including HCV or HBV infection. The efficacy of nivolumab monotherapy was evaluated as a first-line treatment in patients who had not previously received sorafenib or were intolerant and as a second-line treatment in patients with previous disease progression on sorafenib. In this phase I/II study, treatment with nivolumab resulted in substantial tumor reductions and objective response rates (ORRs) of 15%–20% irrespective of the line of therapy. Notably, the disease control rate (DCR) was 58% in the dose-escalation phase and 64% in the dose-expansion phase, which could have positively affected the OS. The median duration of response in both phases of the study suggests that nivolumab might offer lasting responses when other existing therapies have not [40, 41]. The most common treatment-related adverse events in CheckMate 040 were fatigue, rash, pruritus, and increase of serum transaminases. Grade 3/4 treatment-related adverse events occurred in 12 of 48 patients, including adrenal insufficiency, diarrhea, hepatitis, and acute kidney injury. Importantly, the safety profile of nivolumab was consistent among the dose-escalation and expansion cohorts and did

not differ from the observed safety profiles of other tumor entities. Based on the results of CheckMate 040, nivolumab was given accelerated approval by the U.S. Food and Drug Administration on September 23, 2017, for the treatment of patients with HCC in whom sorafenib treatment had failed. And CheckMate 459, a phase III randomized trial of nivolumab monotherapy compared with sorafenib in the first-line setting is ongoing currently.

As we know, patients with chronic viral hepatitis are excluded from almost all clinically initiated studies of PD-1 inhibitors. Hepatic safety events have been reported in virally infected patients with HCC treated with a CTLA-4 inhibitor [42]. The existence of unique safety signals due to viral etiologies was examined in separate cohorts in the CheckMate 040 study, and no new safety signals were found from the dose-escalation phase to the dose-expansion phase.

Other CPIs

Approved CPIs other than nivolumab include pembrolizumab (an anti-PD-1 antibody) and ipilimumab (an anti-CTLA-4 antibody). Other CPIs under development include one anti-CTLA-4 antibody (tremelimumab) and four anti-PD-L1 antibodies (durvalumab, avelumab, atezolizumab, and SHR-1210; Table 1). A trial of tremelimumab in HCC treatment was conducted in 2013 but resulted in more adverse events than were caused by anti-PD-1 antibodies [42]. In 2016, Truong et al. [43] reported a case of metastatic HCC that responded dramatically to pembrolizumab after the failure of sorafenib, in contrast with the above study. Since the CheckMate 040 trial, a phase III trial (CheckMate 459) has been initiated as indicated above, with pembrolizumab in patients who did not respond to sorafenib in a second-line setting, including a phase II trial (KEYNOTE-224, one arm) and a phase III trial (KEYNOTE-240, pembrolizumab vs. placebo). KEYNOTE-224 was first presented by Andrew X. Zhu [44] at ASCO 2018. Patients who failed to respond to sorafenib still received an ORR of 17% (18/104), including 1 complete response, 17 partial response, and 46 stable diseases. Pembrolizumab, as another CPI, was also effective and tolerable in patients with advanced HCC who had previously been treated with sorafenib. Monotherapy with one anti-PD-1 antibody (nivolumab or pembrolizumab) or combination therapy with two CPIs is expected to be successful (Table 1).

CPI COMBINATION THERAPY STRATEGIES IN HCC

As a novel and effective tool, immunotherapeutic interventions have been widely administered in different tumors with impressive results. However, to date, only a few trials have been conducted for HCC, and the results have been contradictory, suggesting that significant improvements are needed. On the one hand, CPIs can enhance the intrinsic tumor suppressive microenvironment of the liver; on the other hand, other antitumor approaches are needed as combinatorial protocols either to stimulate the immune system or to kill or control tumor cells directly. Such combinatorial protocols could theoretically result in a dramatic improvement in efficacy and clinical outcome in patients with HCC [45]. Potential synergistic combinations include CPIs with

Table 1. Clinical trials of antibodies targeting immune checkpoints in hepatocellular carcinoma

Drug	Trial name	Phase	Line of therapy	Design	N	Endpoints	ClinicalTrials.gov	Company	Status
Anti-PD-1									
Nivolumab									
Nivolumab (PD-1 Ab)	CheckMate 040	I/II	1 L/2 L	Cohort 1: dose escalation	42	DLT/MTD	NCT01658878	BMS/ONO	Completed
Nivolumab (PD-1 Ab)	CheckMate 040	I/II	1 L/2 L	Cohort 2: dose expansion	214	ORR	NCT01658878	BMS/ONO	Completed
Nivolumab (PD-1 Ab)	CheckMate 040	I/II	1 L	Cohort 3: nivolumab vs. sorafenib	200	ORR	NCT01658878	BMS/ONO	Completed
Nivolumab (PD-1 Ab) + ipilimumab (CTLA-4 Ab)	CheckMate 040	I/II	2 L	Cohort 4: nivolumab + ipilimumab	120	Safety and tolerability	NCT01658878	BMS/ONO	Completed
Nivolumab (PD-1 Ab)	CheckMate 040	I/II	1 L/2 L	Cohort 5: nivolumab (Child B patients)	49	Safety and tolerability	NCT01658878	BMS/ONO	Recruiting
Nivolumab (PD-1 Ab)	CheckMate 459	III	1 L	Nivolumab vs. sorafenib	726	TTP/OS	NCT02576509	ONO	Recruiting
Nivolumab (PD-1 Ab)		Ib/II		Nivolumab + galunisertib	75	Safety and tolerability	NCT02423343	BMS/Eli Lilly & Co.	Recruiting
Pembrolizumab									
Pembrolizumab (PD-1 Ab)	KEYNOTE-224	II	2 L	Pembrolizumab (1 arm)	100	ORR	NCT02702414	MSD	Completed
Pembrolizumab (PD-1 Ab)	KEYNOTE-240	III	2 L	Pembrolizumab vs. placebo	408	PFS/OS	NCT02702401	MSD	Recruiting
Pembrolizumab (PD-1 Ab)		I	2 L	Pembrolizumab + E7080	30	Safety and tolerability	NCT03006926	Eisai Co., Ltd.	Recruiting
SHR-1210									
SHR-1210 (PD-1 Ab)		II/III	2 L	SHR-1210 every 2 weeks	60	ORR/OS	NCT02989922	Jiangsu HengRui Medicine Co., Ltd.	Recruiting
SHR-1210 (PD-1 Ab) + apatinib or FOLFOX4		II	1 L/2 L	SHR-1210 + apatinib (arm A); SHR-1210 + FOLFOX4 (arm B)	36	Safety and tolerability	NCT03092895	Jiangsu HengRui Medicine Co., Ltd.	Recruiting
Anti-PD-L1									
Durvalumab									
Durvalumab (PD-L1 Ab) + tremelimumab (CTLA-4 Ab)		II	1 L/2 L	Durvalumab (arm A); Tremelimumab (arm B); durvalumab + tremelimumab (arm C)	440	Safety and tolerability	NCT02519348	MedImmune LLC	Recruiting
Durvalumab (PD-L1 Ab)		I	≥2 L	Durvalumab + ramucirumab	114	Safety and tolerability	NCT02572687	Eli Lilly & Co./AstraZeneca	Recruiting
Anti-CTLA-4									
Tremelimumab									
Tremelimumab (CTLA-4 Ab)		II	2 L	Tremelimumab (1 arm, HCV)	20	ORR	NCT01008358	Pfizer	Completed
Tremelimumab (CTLA-4 Ab)		I	1 L	Tremelimumab + TACE or RFA	61	Safety and feasibility	NCT01853618	NCI	Not recruiting

Abbreviations: Ab, antibody; BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T lymphocyte antigen-4; DLT, dose-limiting toxicity; HCV, hepatitis C virus; MSD, Merck Sharp & Dohme; MTD, maximum tolerated dose; NCI, National Cancer Institute; ONO, Ono Pharmaceutical; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TTP, time to progression.

conventional therapies (radiation, chemotherapy, and targeted therapies) and with newer immunotherapies (cancer vaccines and oncolytic viruses, among others; Fig. 1).

CPIs Combined with Locoregional Treatments

HCC typically occurs in a setting of chronic inflammation such as that induced by viral hepatitis. In contrast to other types of cancer, in which surgery, radiation, and chemotherapy dominate the therapeutic landscape, in HCC, locoregional treatments are widely applied, with either curative (ablative procedures) or palliative (arterial chemoembolization) intent.

Studies have shown that the killing of tumors by direct methods can result in the immune system being activated or switched on. The immune system could potentially also recognize and kill the cancer that is left behind, and CPIs could enhance this effect.

Duffy et al. [46] tested one of these drugs (tremelimumab) in combination with ablation in patients with advanced HCC. Thirty-two patients were enrolled in this study, of whom 19 were evaluated for response outside the areas treated directly with ablation, and 5 (26.3%; 95% confidence interval, 9.1%–51.2%) achieved a confirmed partial response. Twelve

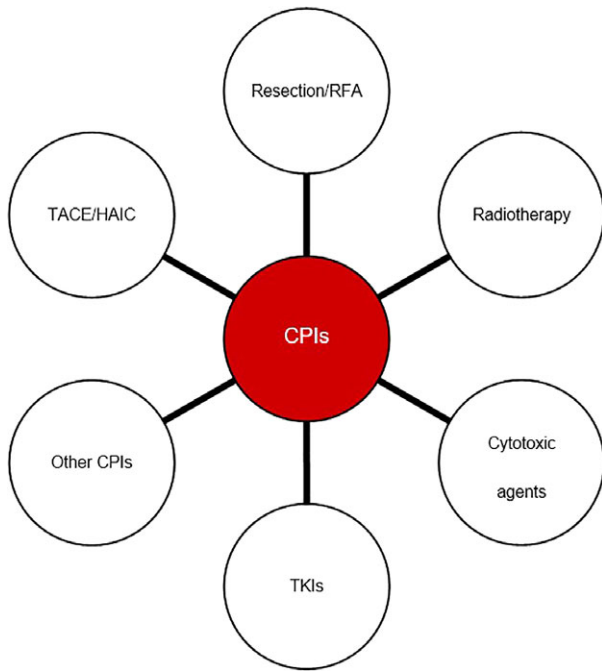


Figure 1. CPI combination strategies.

Abbreviations: CPI, checkpoint inhibitor; HAIC, hepatic artery infusion chemotherapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitor.

of 14 patients with quantifiable HCV experienced a marked reduction in viral load. Interestingly, the two patients who experienced no reduction derived no antitumor benefit from the treatment. This result suggests that antiviral immune responses may act as a surrogate for disease control. Hepatitis B or C is generally an exclusion factor for immunotherapy clinical trials in HCC. Given its global prevalence, this study opted to allow patients with hepatitis B to enroll. Five patients with hepatitis B were enrolled, all of whom were virally suppressed. In these patients, no viral reactivation was seen. Quantitative hepatitis B antigen, which is thought to reflect the number of infected cells as opposed to active replication, was measured and was found to decrease over time in all patients. Although the numbers are small, this finding is also significant and reassuring.

Ablation—by means of alcohol, radiofrequency, microwave, or cryoablation—is considered a curative alternative to surgical resection. TACE is a noncurative procedure for patients with liver-localized HCC for whom surgical resection or ablation is not possible [47]. In the Barcelona Clinic Liver Cancer guidelines, radiotherapy is still not a recommended standard of care in HCC, but it is one of many options in the U.S. National Comprehensive Cancer Network guidelines. These modalities have been shown to induce a peripheral immune response that may be clinically relevant [48–52]. Once an immune response is instigated, it can be potentially amplified by immune modulating agents [53–56]. This study combining immune checkpoint inhibition with ablation in patients with advanced HCC demonstrated intriguing clinical activity. The relative contributions of other interventional procedures need further study,

or perhaps immunomodulation by immune checkpoint inhibition is sufficient for clinical benefit.

CPIs Combined with Antiangiogenetic Therapy

As sorafenib is a VEGF receptor inhibitor, most sorafenib-related studies have focused on its antiangiogenetic effects. However, antiangiogenetic effects may also exacerbate tumor hypoxia, enhance the expression of immune checkpoint molecules, and potentially be the key mechanism of acquired sorafenib resistance, as we noted above. Thus, combining antiangiogenetic therapy with immunotherapy may have a synergistic effect [57].

In a mouse model with subcutaneous implanted tumors, Yasuda et al. [58] tested a combination therapy of anti-VEGFR2 and anti-PD-1 antibodies. They showed that combination treatment can enhance immune responses by increasing IFN- γ , TNF- α and granzyme B production levels. In another mouse model, Chen et al. [59] proposed a strategy combining sorafenib with CPI in HCC. They found that sorafenib increased tumor hypoxia and subsequently induced the expression of SDF1 α and the accumulation of myeloid-derived suppressor cells (MDSCs) in HCC. AMD3100, an inhibitor of the CXCR4 receptor, can also enhance the inhibition of tumor growth when combined with sorafenib. Triple combination therapy with sorafenib, AMD3100, and CPI also enhanced the intratumor infiltration of activated CTL and significantly delayed tumor growth and metastasis. Our ambition is to translate mouse model results with a powerful theoretical basis into clinical practice in HCC. Recently, a clinical study of the combination of ipilimumab with bevacizumab reported promising initial efficacy in patients with melanoma [60]. At least three phase I or II studies have been initiated in other types of tumors.

Lenvatinib is an oral multikinase inhibitor that selectively inhibits the kinase activities of VEGFR1–3, in addition to other proangiogenic and oncogenic pathways, including FGFR1–4, PDGFR- α , and RET and KIT proto-oncogenes [61–63]. Lenvatinib was approved as a single agent for the treatment of radioiodine-refractory differentiated thyroid cancer [64] and in combination with everolimus for the treatment of advanced RCC after one prior antiangiogenetic therapy [65]. A phase III trial of lenvatinib versus sorafenib in the first-line treatment of patients with unresectable HCC (the REFLECT study) was presented in ASCO 2017 [66]. Lenvatinib has demonstrated noninferiority versus sorafenib in OS (13.6 months for lenvatinib vs. 12.3 months for sorafenib) and achieved statistically significant and clinically meaningful improvement in PFS, time to progression, and ORR. Based on the REFLECT study results, lenvatinib may be a potential treatment option in patients with advanced HCC. As an antiangiogenetic agent, whether lenvatinib can be combined with CPIs in tumor therapy is uncertain. Interestingly, a promising result from a phase II RCC cohort study combining lenvatinib with CPI was highlighted at the European Society for Medical Oncology 2017 Congress in Madrid [67]. Patients with metastatic clear cell RCC who had been treated with zero to two prior lines of systemic therapy were administered lenvatinib 20 mg orally every day plus pembrolizumab 200 mg intravenously every 3 weeks (21-day cycles). In 30 patients eligible for response evaluation, ORR was 83% and DCR was

100%. This finding offers further support for the ongoing phase III trial comparing lenvatinib plus pembrolizumab, lenvatinib plus everolimus, and sunitinib monotherapy in a first-line setting for the treatment of metastatic clear cell RCC (ClinicalTrials.gov identifier, NCT02811861). Similar notable antitumor activity and acceptable safety profiles were also found in endometrial cancer [68] and malignant melanoma (ClinicalTrials.gov identifier, NCT03006887). Results of three phase Ib studies related to CPIs combined with antiangiogenic agents in HCC [69–72] were presented in posters at ASCO 2018 (abstract 4074 s–4076) with promising ORR (ranging from 42.3% to 65%), including lenvatinib plus pembrolizumab, atezolizumab plus bevacizumab, and SHR-1210 plus apatinib. An open-label phase IIb trial of lenvatinib plus pembrolizumab in HCC (ClinicalTrials.gov identifier, NCT03006926) sponsored by Eisai Co., Ltd., and another phase II trial of SHR-1210 plus apatinib in Chinese patients with HCC sponsored by Jiangsu HengRui Medicine Co., Ltd., have also been initiated (ClinicalTrials.gov identifier, NCT03092895).

CPIs Combined with Chemotherapy

HCC is known to be highly refractory to conventional systemic chemotherapy because of its heterogeneity and multiple etiologies. The EACH study [73] contradicted this traditional opinion. Although the study did not meet its primary endpoint, it found a trend toward improved OS with FOLFOX4, along with increased PFS and ORR, especially in Asian patients [74]. In addition to direct cytotoxic effects on cancer cells similar to those of other traditional chemotherapy agents, oxaliplatin can induce immunogenic cell death and activate an antitumor immune response [75]. Possible mechanisms include dendritic cells activation and the expression of costimulatory molecules, the enhanced cross-priming of CD8-positive (CD8+) T cells, the promotion of the antitumor CD4-positive T-cell phenotype, the downregulation of MDSC and regulatory T-cell activity, the promotion of tumor cell death via lytic receptors or pathways, increased serum inflammatory cytokines, and proinflammatory changes in the tumor microenvironment.

These studies provide a rationale for the exploration of chemotherapy in combination with CPIs, especially in the Asia-Pacific region. Ipilimumab and nivolumab have been explored in combination with chemotherapy (carboplatin-paclitaxel) in several trials [76], but whether CPIs can combine with oxaliplatin in HCC is still to be explored. The potential synergistic roles of oxaliplatin with immune checkpoint blockades has been confirmed by Wang et al. [77] in a colorectal cancer animal model. A phase II trial of SHR-1210 combined with FOLFOX4 in Chinese patients with advanced HCC has been initiated (ClinicalTrials.gov identifier, NCT03092895).

CPIs Combined with a Mammalian Target of Rapamycin Inhibitor

Li et al. [78] revealed that HCC cell lines and clinical tissues frequently contain cancer subpopulations that overexpress PD-1, and PD-1 overexpression enhances tumor growth in the absence of an immunological environment. In contrast, PD-1 blockade and PD-1 knockdown in vitro and vivo inhibit tumor growth independently of adaptive immunity. The major underlying mechanism is the binding of PD-1 to two

downstream mammalian target of rapamycin (mTOR) effectors, eukaryotic initiation factor 4E, and ribosomal protein S6, thereby promoting their phosphorylation. More importantly, combining mTOR inhibitors with anti-PD-1 provides more lasting and synergistic tumor regression than either agent alone, each of which presents only modest efficacy. Therefore, targeting mTOR pathways in combination with PD-1 may result in increased antitumor efficacy in patients with cancer.

Multiple Immune Checkpoint Blockade

Simultaneously blocking both PD-1 and CTLA-4 signals has been another impressive strategy in solid tumors and is currently being used to achieve a stronger effect than monotherapy. The advantages of this strategy have been proved in malignant melanoma [79]. Based on the rationale that blockade of the PD-1/PD-L1 pathway cannot be effective if CD8+ T cells do not exist in the tumor microenvironment, a combination with CTLA-4 blocking might increase the number of activated CD8+ T cells [80]. Indeed, such a combination trial for the treatment of HCC is in the early stages. As shown in Table 1, a phase I/II trial is currently underway comparing nivolumab, ipilimumab, and their combination at varying doses and intervals. A similar three-arm trial has also begun to enroll patients to compare the efficacy and safety of combination therapy consisting of durvalumab and tremelimumab with the corresponding monotherapies (Table 1). The results of these trials are eagerly awaited.

FUTURE PERSPECTIVES AND CHALLENGES

The emergence of CPIs in the last decade has offered great promise in the treatment of a rapidly expanding spectrum of solid tumors including NSCLC, RCC, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer. If cytotoxic agents are considered the first stage of anticancer therapy and molecular targeted inhibitors the second, we are now approaching the third stage with CPIs. CPI-based strategies will soon be a main approach in anticancer treatment for HCC, and we will observe the rapid advances in the therapeutic use of CPIs, even in an adjuvant setting, with great interest, especially in China.

However, even with immune checkpoint blockade, a substantial proportion of patients fail to derive clinical benefit, and as yet, few predictive biomarkers have been found to select patients with HCC who may benefit. In virus-related HCC, especially HBV-related HCC, whether CPIs can control virus relapse should be further investigated. Combination strategies involving conventional therapies and immunotherapies are needed to increase clinical benefit and minimize adverse toxicities with regard to the underlying liver disease.

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DISCLOSURES

The authors indicated no financial relationships.

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