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Immune checkpoint inhibitor therapy for hepatocellular carcinoma

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Abstract

Liver cancer is the third most common cause of cancer-associated death. Advances in the last decade have provided more options for treating hepatocellular carcinoma. The use of immune checkpoint inhibitors represents a leap forward and broadens the armamentarium for clinicians. In this article, we provide a state-of-the-art review of molecular therapy. We also detail the mechanisms of checkpoint inhibitor therapy, which blocks the interaction of programmed cell death receptor protein with programmed cell death ligand, reducing the immune checkpoint activity on regulatory T cells, thereby inhibiting tumor cell growth.

Keywords Hepatocellular carcinoma, checkpoint inhibitors, immunotherapy

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Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer. With nearly one million new cases diagnosed annually worldwide, HCC comprises a significant portion of the global cancer burden [1]. The high prevalence and increasing incidence of HCC over the recent decades, along with the limited effective treatment options, has placed HCC as the fourth most common cause of cancer-related death worldwide [2]. Despite the recent addition of new therapeutic agents for treating advanced inoperable HCC, the 5-year survival rate remains at 18% [3]. The incidence of HCC fluctuates geographically according to the variable prevalence of underlying risk factors [4]. The global distribution of HCC is such that 72% of cases occur in Asia, with more than 50% being from China [4]. Of the remainder, 10% of cases occur in Europe, 7.8% in Africa, 5.1% in North America, 4.6% in Latin America, and 0.5% in Oceania [4].

The most salient risk factor for HCC is liver cirrhosis deriving from any etiology, as the likelihood of malignant transformation increases in settings of chronic liver injury [5]. Therefore, regions with a higher prevalence of cirrhosis are prone to development of HCC. The most notable etiology of liver cirrhosis worldwide is viral hepatitis [1]. Geographic areas bearing the highest burden of HCC include East Asia and Africa, where the endemic prevalence of viral hepatitis creates a predisposition for chronic liver disease and consequent susceptibility to progression to HCC [1]. Other common causes of cirrhosis include chronic alcohol abuse, exposure to aflatoxins, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH) [6]. Hepatitis B virus is the principal cause of liver cancer in the world, responsible for an estimated 33% of HCC deaths overall. In regions such as Africa and East Asia, this number is estimated to be 60%. In the western world, only 20% of HCC deaths are attributable to hepatitis B virus infection [4]. Chronic hepatitis C has historically been the most common underlying liver disease etiology in the western world, but this is expected to change in coming years, as NAFLD and NASH become the most pervasive mechanisms of chronic hepatocellular damage [7]. While patients with NAFLD have a lower risk of HCC development than those with viral hepatitis infection, approximately 6 million people in the USA have some form of NAFLD or NASH [4]. A lower risk of HCC development

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applied to an increasing population with NAFLD or NASH yields a concerning proportion of the population at risk.

Widespread implementation of hepatitis B vaccination has assisted in reducing the global viral burden of hepatitis B [7]. Additionally, the advancing efficacy of hepatitis C treatment has played a role in reducing the proportion of HCC cases resulting from viral hepatitis [4]. While HCC incidence has decreased in certain regions, as a result of improved prevention and treatment of hepatitis B and C viruses, the global incidence of HCC still continues to climb. Notably, the incidence of HCC is rising particularly in Europe and the USA [4].

The rise of HCC in the developed countries is probably attributable to the rise in disorders related to the metabolic syndrome [8]. Unfortunately, the advances in reducing viral hepatitis disease burden in endemic areas is negated by the rise in metabolic syndrome-related liver disease, such as NAFLD, in the developed countries [7].

Understanding the shifting epidemiologic profile is crucial for identifying populations at risk and working to prevent the progression of the disease. As the prevalence of obesity, type 2 diabetes and metabolic syndrome-related conditions continues to rise, so does the incidence of NAFLD [7]. NAFLD is an additional known agent of hepatocellular injury and risk for HCC [1]. A retrospective cohort study of 271,906 patients demonstrated that the risk of HCC increased with each additional metabolic syndrome trait [9]. More specifically, HCC risk was 2.6-fold higher in patients who had NAFLD along with concurrent diabetes, obesity, dyslipidemia and hypertension, compared to patients with isolated NAFLD [9]. The changing epidemiologic landscape of HCC etiologies suggests that strategies to combat the rising prevalence of obesity and diabetes may play a significant role in decreasing the incidence of NAFLD, and ultimately assist with reducing the HCC burden in the future.

The direct and indirect economic burden of HCC is extensive at present, and is expected to increase in concordance with the rise in the incidence and prevalence of HCC. Additionally, the introduction of various new and expensive therapies to the forefront of HCC therapy is likely to further increase the economic toll of HCC [3]. A systematic literature review quantified the direct costs to patients in the USA undergoing therapy for HCC and found that the median estimated expense is $176,456 per patient per year [3]. The monetary cost of care varies geographically, but amounts to an extensive economic burden worldwide. In addition to the substantial direct costs of therapy and patient care, the indirect costs—including economic losses from persons affected by HCC unable to work, the cost of traveling for therapy, among other expenses—further contribute to the cost burden of HCC [3]. Despite the high costs of therapy and the introduction of several promising new chemotherapy agents available for HCC management, outcomes in advanced unresectable HCC are not favorable. The Annual Report to the Nation on the Status of Cancer for 2020 listed HCC as 1 of 5 cancers reported to be increasing in incidence [10]. HCC is the second most common cause of cancer-related death after lung cancer [10]. A multitude of factors impact the relatively poor outcomes seen in HCC. A retrospective study using Surveillance, Epidemiology, and End Results (SEER) data examined the relationship between stage of HCC at diagnosis and socioeconomic status [11]. Results found that patients with lower incomes (<$40,000 annually) faced higher odds of HCC diagnosed at advanced stages (odds ratio 1.15, 95% confidence interval [CI] 1.01-1.32; P=0.03) [11]. Diagnosis at advanced stages limits treatment efficacy, because of the late intervention and higher chance of metastasis [11]. Therefore, mortality rates across income groups followed suit, with patients of lower income status shouldering a higher mortality rate (hazard ratio 1.23, 95%CI 1.16-1.31; P<0.001) compared to higher income brackets (>$70,000) [11].

These results suggest that socioeconomic and demographic profiles may play a role in predicting outcomes of HCC [11]. The introduction of new and expensive medications to the market may result in growing treatment disparities within the population, as access to cutting-edge new therapy is often available exclusively to certain subsets of the population. Still, regardless of demographic profile and epidemiologic factors, the survival percentages remain unfavorable, with an average 5-year survival of 18% [3].

Discussion

HCC: approach to therapy

The National Comprehensive Cancer Network provides a framework for current therapeutic guidelines for HCC. Once the diagnosis of HCC has been confirmed, it is important to conduct a comprehensive evaluation [12]. This evaluation must include imaging studies to visualize the lesion, a thorough history of the presenting illness as well as a viral hepatitis panel to assist in determining the etiology [12]. Additionally, laboratory testing is crucial to glean information about the synthetic function of the liver, as well as obtaining parameters for calculation of a Child-Pugh score [12]. The Child-Pugh score uses the parameters of encephalopathy, ascites, albumin, prothrombin time and bilirubin to calculate a score correlated with the operative risk [12]. Class A is described as a score of 5-6 points, and indicates a good operative risk [12]. Class B refers to a score of 7-9 points, and Class C to 10-15 points, with operative risks of moderate and poor, respectively [12]. These elements of the evaluation will factor into determining whether the patient is a candidate for liver resection or transplant. The Milan criteria provide a framework to assess a patient's suitability for liver transplantation [13]. This information contributes to formulating a therapeutic regimen, as candidacy for surgical intervention requires certain parameters to be met. If a patient has inadequate hepatic reserve, such that surgical excision of the cancer legion plus margins would leave the patient with insufficient hepatic tissue for survival, the cancer is considered inoperable [12]. Other reasons for deeming HCC inoperable include inaccessible or precarious location of the HCC around a major blood vessel [12]. Additionally, to be considered for surgical excision, a patient must be deemed fit for major surgery. Considering that most cases of HCC develop in a setting of chronic liver disease and cirrhosis, surgical

excision is not a possibility in the majority of HCC cases, given the previously poor health status of affected patients who have a low baseline hepatic synthetic functional reserve [14]. A chronically impaired liver typically correlates with notable laboratory values indicating thrombocytopenia, prolonged prothrombin time (high international normalized ratio), low albumin, among various other possible derangements. A high risk of gastrointestinal bleeding based on the above concerns plays a major role in determining which therapeutic options may be considered for an individual patient. Bleeding may ensue as a result of portal hypertension causing ruptured varices, or from the impaired ability to clot a minor lesion. The risk of blood loss and coagulopathies, as well as low albumin, suggesting a poor baseline state of health and therefore a risk of a poor outcome, present a major challenge specific to HCC, as various other solid tumor lesions rely in part on surgical excision as a mainstay of treatment. The addition of treatments with different mechanisms of action provides alternative options for patients who do not meet criteria for the limited previously available options, as well as those refractory to first-line therapies. Expanded criteria for determining treatment plans were set out by the Barcelona Clinic Liver Cancer staging system [14].

Standard chemotherapeutic options

The current therapeutic approach to HCC is multifactorial and consists broadly of surgical therapies, nonsurgical local/regional directed therapies, and systemic therapies. Surgical therapies include liver resection and transplantation [15]. Nonsurgical local/regional directed therapies include radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), microwave ablation (MWA), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) [16]. RFA employs oscillating electrical currents surrounding a strategically placed electrode, which generates resistive heating and hyperthermia in tissue [16]. Though more research is needed to harness the full therapeutic potential of RFA, Galanakis *et al* reported that, in the early stages of disease, RFA or MWA are equivalent to surgical resection [17]. Though numerous individual studies report promising results surrounding use of RFA, a Cochrane meta-analysis conducted by Weiss *et al* found that surgical intervention was superior to RFA when considering survival [18]. Regarding TACE and TARE, Galanakis *et al* suggested that the limitations of each individual therapy may be augmented by combination therapies [16]. Tandem therapy has shown superior outcomes to monotherapy, with improved overall survival statistics and no significant differences in complications [16]. Analysis by Peng *et al* supports the use of combination therapy, reporting that RFA and TACE were superior to RFA alone for patients with HCC less than 7 cm, leading to improved survival [19]. Additional percutaneous targeted therapies include PEI, MWA, laser therapy, high-intensity focused ultrasound, stereotactic body radio-ablation therapy, and cryoablation [13]. The concept of nonsurgical locoregional therapeutic techniques is the precise delivery of cytotoxic agents to a specific tumor target, resulting in death to tumor cells with preservation of surrounding healthy tissue [13].

Systemic therapy includes chemotherapy, molecular target-directed therapy (e.g., multikinase inhibitors), and immunotherapy with immune checkpoint inhibitors (ICI) [20].

Surgical intervention is a mainstay of treatment for any solid tumor, yet therapy for HCC requires a multidisciplinary approach to therapy, employing multiple different tactics. Even if surgical criteria are met and resection of cancerous tissue is successfully completed, patients often suffer recurrences [21]. While the mechanism of recurrence following resections with clean margins is not fully understood, one hypothesis proposes that preexisting subclinical micro-foci of cancerous cells exist in a diffusely damaged and cirrhotic liver [21]. Therefore, resection alone is typically not adequate in the treatment of HCC and the integration of nonsurgical with systemic neoadjuvant therapies is integral to successful therapy and prolonged survival. Nonsurgical local/regional therapies can also be paired with surgical interventions [13].

Exploration of locoregional therapies paired with surgical interventions is underway, as is the study of locoregional therapies combined with multikinase inhibitors [22]. The combination of locoregional therapies with ICI therapies remains to be investigated, and is a likely future direction of progress in immunotherapy. As the data from ICI therapy in the context of HCC become more robust, a necessary direction of research to understand the true potential of ICI therapy is to pursue investigations of its combination with locoregional therapies.

Advances in the therapy for HCC are most notably occurring in the realm of systemic therapy. The SHARP trial marked a major turning point in HCC therapy. Prior to the SHARP trial, there were no systemic chemotherapy agents in existence for HCC [23]. This trial demonstrated the multikinase inhibitor sorafenib as the first systemic chemotherapy agent shown to increase the overall survival in HCC [24]. The SHARP trial was a phase III double-blinded, placebo-controlled trial, where 602 patients with advanced HCC were given either the multikinase inhibitor sorafenib or placebo [17]. Patients were randomly assigned and had no previous systemic therapy. This study demonstrated a 3-month longer median survival time for those receiving sorafenib compared to placebo [17]. A systematic review investigating the mechanism of action behind the success of sorafenib suggests modulation of the tumor microenvironment, as well as various immune cells [25]. Since the incorporation of sorafenib into HCC therapy, an array of new therapeutic options has been the focus of research and inclusion into HCC therapy regimens.

HCC is a complex form of cancer. The wide variety of pathogenic processes causing cirrhosis is likely to contribute to the large number of genomic alterations observed [26]. Common genetic aberrations in hepatocellular signaling cascades include mutations to genes involved in cellular growth signaling pathways. Notable genes include endothelial growth factor receptor, as well as Ras/ERK, PI3K/MTOR, HGF/MET, Wnt, Hedgehog, and other apoptotic signaling components, including those outlined in Table 1 alongside corresponding

therapeutic interventions [26]. While each mutation holds potential for chemotherapeutic molecular targeting, the number of mutations also contributes to the challenge of treating HCC.

Trials of molecular therapies were aimed at the various genetic markers implicated in HCC. The EVOLVE-1 trial investigated the use of everolimus, an mTOR inhibitor, in patients with advanced HCC after failed therapy with sorafenib [27]. Unfortunately, no significant survival difference was observed [27]. Similarly, investigation of brivanib, a vascular endothelial growth factor receptor inhibitor, failed to demonstrate any significant findings in the BRISK-PS study [28].

Other multikinase inhibitor therapies, such as cabozantinib and regorafenib, were investigated in the CELESTIAL trial and RESOURCE trial, respectively. Cabozantinib resulted in severe and common adverse effects and is not recommended as a first-line treatment because of its low tolerability [29]. Though many trials failed to improve survival, regorafenib demonstrated a potential to enhance outcomes for those already taking sorafenib [30]. Additionally, the REFLECT trial found that lenvatinib was noninferior to sorafenib in terms of overall survival, while having similar safety and side effect profiles [31].

Other notable studies include REACH-2, a phase III second-line, randomized, double-blind study comparing ramucirumab with placebo, as well as studies on apatinib in a Phase II first-line randomized, multicenter, open-label trial [32]. Ramucirumab is a monoclonal antibody that functions by inhibiting angiogenesis, making it a useful adjunctive therapy for various forms of cancer [33]. Tremelimumab, a monoclonal antibody acting as a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, has also been investigated as a therapeutic option, demonstrating potential antiviral effects in HCC patients with hepatitis C virus [34]. Results support the need for further research to generate more data on the use of tremelimumab [34].

The next breakthrough in systemic therapy development developed through data from the CheckMate 040 study, which demonstrated the potential utility of checkpoint inhibitors in the treatment of HCC [35]. The goal of this trial was to evaluate the safety and efficacy of nivolumab [35]. While previous research had focused on molecular target-directed therapy, specifically multikinase inhibitors, CheckMate040 highlighted the potential of checkpoint inhibitor therapy for treatment of HCC.

Table 1 Landmark clinical trials in the treatment of hepatocellular carcinoma

Study	Interventions	Molecular targets	Overall survival (months)
SHARP2007	Sorafenib vs. placebo	BRAF VEGFRs PDGFR KIT	Sorafenib: 10.7 Placebo: 7.9
CheckMate040	Nivolumab	PD-1	15.0
KEYNOTE224	Pembrolizumab	PD-1	12.9
CELESTIAL	Cabozantinib	VEGFRs KIT RET MET	8.0
REACH-2	Ramucirumab	VEGFR2	7.3
REFLECT	Lenvatinib vs. sorafenib	VEGFRs FGFRs PDGFRa KIT RET	Lenvatinib 13.6 Sorafenib 12.3
IMBrave150	Atezolizumab + bevacizumab	PD-L1, VEGF	12.0

PDGFR, platelet derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor

Table 2 Child-Pugh score and FDA-approved systemic therapy options

Child-Pugh class A ONLY	Child-Pugh classes A and B	Child-Pugh class B	Child-Pugh class C
Atezolizumab + bevacizumab			
Sorafenib Lenvatinib nivolumab + ipilimumab pembrolizumab	Sorafenib		
Regorafinib Cabozantinib Ramcirumab Lenvatinib	Sorafenib		
	Nivolumab	Nivolumab FOLFOX	

Checkpoint inhibitor therapy

In recent years, several new biologic therapies tested in clinical trials have demonstrated a potential for increased progression-free survival and overall survival (Table 2) [20]. The advancements in HCC treatment are largely due to the application of ICI therapy. Integrating ICI therapy into the clinical management of various malignancies has changed the landscape of cancer treatment at large [36]. The proven efficacy of ICI therapy in treating various other forms of malignancy has led to its application in the setting of HCC [27]. Prior to the introduction of ICI systemic chemotherapy agents for the treatment of HCC, the multikinase inhibitor sorafenib was the mainstay of systemic treatment, along with surgical intervention when possible [26]. Therefore, most research compares new pharmaceutical agents with the standard of care in systemic therapy.

Understanding the pathophysiology of HCC is important for developing tactical treatment strategies when approaching this complex form of cancer. The environment of chronic liver disease in which HCC frequently develops results from repeated

pathologic insult to hepatic parenchyma. Chronic injury results in long-term exposure to inflammatory molecules [37]. A prolonged inflammatory state leads to impairment of a delicate balance of immunological factors [37]. The immune tolerance system is comprised of many different types of cells and cellular components, including antigen-presenting cells, T cells, immune checkpoint proteins, and influence by circulating inflammatory cytokines [37].

In a physiologic state, the system fluxes in balance, destroying unhealthy cells and preserving functional healthy cells [37]. In chronic liver disease, inflammation and tissue injury cause dysfunction and upregulation of immunotolerant signals, thus diminishing immune responses and reducing the destruction of aberrant or damaged cells [37]. This state of diminished ability to mount an immune response is referred to as T-cell anergy [37]. The immune system in this exhausted T-cell state is not able to effectively detect and thwart abnormal cell growth, rendering the patient susceptible to HCC [37]. The concept of ICI therapy is to reestablish a balanced state in the immune tolerance system. Restoring immune function can be accomplished through priming immunological components to regain function and decrease immunotolerance, thus recognizing the neoplastic cells as a threat and destroying the HCC.

ICI therapies, also known as biologics, are a means of cancer treatment that enlist the patient's own immune system to destroy neoplastic cells. Checkpoint inhibitors are a class of systemic chemotherapy agents that function by modulating immune system cellular interactions with tumor cells [28]. This is accomplished by directing monoclonal antibodies towards cellular checkpoint proteins [38]. Checkpoint proteins must be inactivated in order for the immune system to recognize atypical cells as a threat and trigger an immune response [29]. ICIs are monoclonal antibodies that prevent the interaction between checkpoint proteins on cancer cells and checkpoint proteins on immune cells [37]. Subsequently, immune cells recognize the cancerous cells as a threat, and mount an immune response [39]. The ability to mobilize and focus the existing mechanisms of the immune response towards the destruction of cancer cells is a remarkable application of pharmaceutical technology.

Many ICIs target the programmed cell death 1 cellular pathway (Fig. 1) [39]. The 2 main molecules in this pathway are programmed cell death receptor protein (PD-1), found on the surface membrane of immune cells, and programmed cell death ligand (PD-L1), expressed physiologically on cells. Common PD-1 inhibitors include nivolumab and pembrolizumab, and the most notable PD-L1 inhibitor is atezolizumab [40]. At the molecular level, these checkpoint inhibitors mainly function by blocking the PD-1 receptor on T cells, or PD-L1 ligand on cancer cells. Preventing the PD-1 and PD-L1 interaction allows the T cell to recognize the cancer cell as a threat [39]. Expression of PD-L1 is one common mechanism by which cancer cells elude destruction by the immune system [38]. Therefore, PD-1 and PD-L1 checkpoint proteins have become a popular molecular target for biologic chemotherapy development. Similarly, increased expression of CTLA-4 can further impair T-cell function [31]. Therefore, CTLA-4 is an additional immune checkpoint protein that is a target for ICI therapy [41].

CTLA-4 is an inhibitory coreceptor found on the surface of certain immune cells. It impairs T-cell activation and proliferation, and neoplastic cells often express CTLA-4, leading to a diminished immune response. Inhibition of CTLA-4 enables T cells to function more effectively. This process is described in Fig. 2. The most widely used ICI targeting CTLA-4 is ipilimumab [34]. ICI therapy has demonstrated the ability to restore T-cell function in various other malignancies through inhibition of PD-1/PD-L1 and CTLA-4 [27]. The

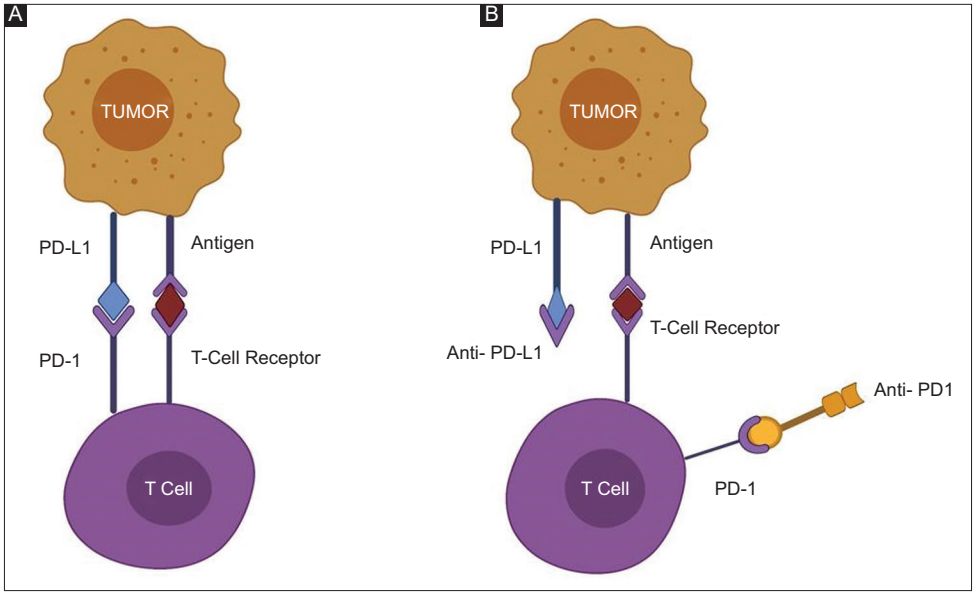

Figure 1 Schematic diagram of (A) PD-1 protein on T-cells binding to PD-L1 protein on the tumor cells, which inhibits the destruction of tumor cells. (B) Anti PD-1 and anti-PD-L1 interventions, known as immune checkpoint inhibitors, inhibit binding between tumor cells and T cells, which allows T-cell-mediated killing of tumor cells

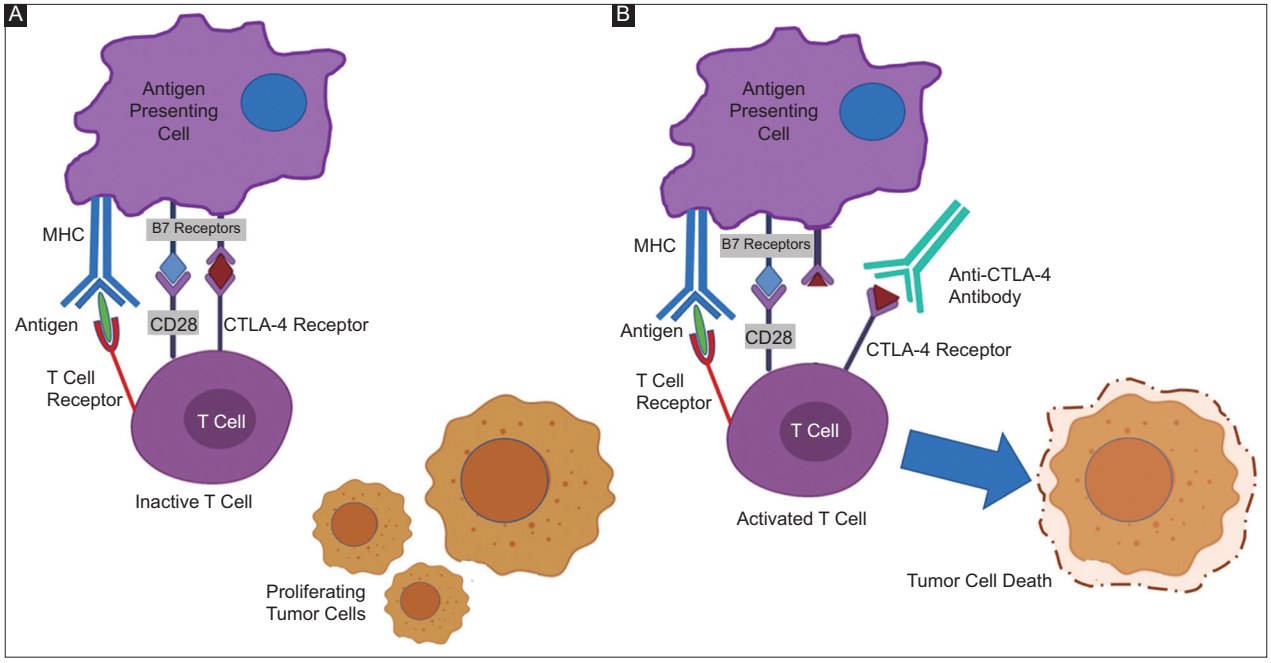

Figure 2 Schematic diagram of (A) cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor on T cells binding to B7 receptors on antigen-presenting cells, which inhibits destruction of tumor cells. (B) Anti-CTLA-4 antibodies comprise another form of immune checkpoint inhibitor. These antibodies inhibit binding between antigen presenting cells and T cells, which allows T-cell-mediated killing of tumor cells

focus of research is primarily on PD-1 and PD-L1 inhibition rather than CTLA-4, as blockade of PD-1 and PD-L1 proteins demonstrated objective response rates up to 20% higher in the treatment of advanced HCC [37].

Integration of ICI therapy into the clinical management of HCC has demonstrated strong response rates and improved overall mean survival in various landmark studies. Notable studies include CheckMate 040, a phase 1/2, open-label, non-comparative, dose escalation and expansion trial that examined the therapeutic potential of nivolumab, a monoclonal antibody targeting inhibition of PD-1 checkpoint protein [35]. In 2017 nivolumab was among the first FDA-approved additions to sorafenib in systemic therapy for HCC [35]. Findings indicated that nivolumab had therapeutic potential in the treatment of HCC [35]. While the majority of systemic therapies are available for Child-Pugh class A only, nivolumab monotherapy is also approved for Child-Pugh class B [41]. However, the Checkmate 459 trial later found that nivolumab monotherapy failed to demonstrate advantage over sorafenib in Child-Pugh class A, and is therefore reserved for Child-Pugh class B as an alternative therapy option in cases where patients were not candidates for multikinase inhibitors [41]. Options for Child-Pugh classes B and C remain very limited, as shown in Table 1.

Nivolumab was followed by FDA approval of pembrolizumab, also a PD-1 inhibitor. It is worth noting that nivolumab and pembrolizumab have not yet received approval from the European Medicines Agency (EMA). The KeyNote 224 study, conducted by Zhu *et al*, examined the safety and efficacy of pembrolizumab, finding that it was both safe and tolerable for patients previously treated with sorafenib for advanced HCC [42]. Further research in 2 Phase III clinical trials followed, leading to approval of pembrolizumab as a second-line treatment for HCC [42]. Although Phase III trials of nivolumab monotherapy as a first-line agent and pembrolizumab monotherapy as a second-line agent failed to demonstrate statistically significant improvements in outcome, variability was noted among the data, suggesting that monotherapy with these agents may be effective in certain subsets of patients [20].

While monotherapy with ICIs is an important step towards understanding their therapeutic potential, major advances in therapeutic outcomes have come from studies implementing combination therapies, such as additional arms of CheckMate 040 that used nivolumab + ipilimumab to target both PD-1 and CTLA-4 checkpoint inhibitor molecules [32]. An arm of the CheckMate 040 randomized clinical trial examined the efficacy and safety of combination therapy with nivolumab and ipilimumab in patients with advanced HCC who had previously been treated with sorafenib [43]. This trial found that the nivolumab plus ipilimumab combination showed manageable safety, stable responses, and potential for improved clinical outcomes.

The IMBrave150 study paired atezolizumab + bevacizumab in combination therapy, targeting the PD-L1 checkpoint inhibitor protein and the vascular endothelial growth factor kinase receptor [32]. The IMBrave150 study is among the most successful advances in HCC treatment, and the results piloted the current first line of systemic therapy. The IMBrave150 study compared combination therapy with atezolizumab and bevacizumab vs. standard monotherapy with sorafenib in patients with unresectable HCC and no previous systemic treatment [44]. Findings showed better

overall and progression-free survival outcomes with the use of atezolizumab and bevacizumab combination therapy compared to sorafenib, with an improvement in 1-year survival rate from 54.6-67.2% [44].

Future directions in the treatment of HCC may also combine multikinase inhibitors with ICIs. Research is underway with combination therapy pairing lenvatinib and pembrolizumab in therapy for patients with unresectable HCC [44]. This Phase Ib study investigated the immunomodulatory properties of lenvatinib, a multikinase inhibitor, when paired with pembrolizumab, an ICI inhibitor of PD-1 [32]. The investigators report that combination therapy with lenvatinib and pembrolizumab show promising anti-tumor activity in unresectable HCC [44]. For patients with advanced, unresectable HCC, systemic therapy options were previously limited, and the outcomes have not been favorable. The advent of immunotherapy as a means for treating HCC holds promise for more effective therapy options becoming available for treating this highly prevalent disease. There is evidence suggesting that ICI therapy benefits certain subsets of patients more effectively than others. Unfortunately, the identification of specific biomarkers associated with implications for therapeutic impact have yet to be identified [45]. The most notable biomarker related to HCC is α-fetoprotein, but many new markers of inflammatory processes at the molecular level are currently being investigated.

A notable and serious limitation of the therapeutic potential of ICIs is described by Pfister *et al*, whose study generated data lending insight into the role of T cells specifically in a setting of NASH/NAFLD [46]. These data indicate that ICI therapy in HCC cases developing from NASH/NAFLD is not only ineffective, but also associated with poor outcomes [46]. This finding is problematic when considering the shifting epidemiologic landscape of HCC, where NASH/NAFLD is becoming the pervasive mechanism of chronic liver inflammation. A subsequent study further suggested there may be a relationship between therapy selection and the etiology of inflammatory processes. This multicenter retrospective investigation by Hiraoka *et al* found that lenvatinib may be a suitable option for HCC therapy, irrespective of HCC etiology [47]. Biomarker associations and identification of suitable candidates for different therapies remain ambiguous, despite guidelines set forth in the Barcelona Clinic Liver Cancer algorithm [48]. Nevertheless, studies are demonstrating more concrete evidence that combination therapies are more efficacious than monotherapy with ICI agents [36]. This innovative approach to cancer therapy holds potential, yet studies are finding variable results [39]. Further investigation of biomarkers is required to make predictions about ICI responses on an individual patient basis [39].

Cost effectiveness

The advent of ICIs has profoundly influenced the field of cancer therapy. As ICI use grows to play an established role in the clinical management of HCC, it is important to consider the cost. Understanding costs is a salient component of bringing new therapies to the forefront of clinical care.

Chiang *et al* recognized the success of the IMBrave150 trial, which showed that combination therapy with atezolizumab plus bevacizumab can achieve statistically significant improvement in survival outcomes compared to sorafenib monotherapy [49]. The same investigators assessed the combination therapy from the USA payer perspective, analyzing the data from the standpoint of 3 main outcomes: life years, quality-adjusted life years, lifetime costs, and incremental cost-effectiveness ratio [49]. Importantly, the atezolizumab plus bevacizumab combination showed a 44% gain in quality-adjusted life years, with an additional cost of $79,074 [49]. The data revealed that atezolizumab plus bevacizumab is cost-effective in some scenarios but not others [49]. This investigation suggests that cost-effectiveness could be achieved by either instituting a maximum duration of therapy of one year, or reducing the dosage of atezolizumab plus bevacizumab to less than 10 mg/kg [39]. Though not yet deemed cost-effective in all scenarios, analyses of this kind suggest that the use of ICI has the potential to become a mainstream and cost-effective therapy for HCC [49]. In addition to cost considerations, further research is needed to identify biomarkers that may relate to therapeutic effectiveness and assist with streamlining therapy in contexts where a favorable outcome is reliably predicted [26]. Better understanding of biomarkers should also help reduce the cost of care in the future through more focused therapeutic interventions.

An additional cost consideration of ICI therapy emerges in the form of immune-related adverse events [50]. Instead of the traditional chemotherapeutic paradigm of infusing therapy to induce apoptosis in all cells with high mitotic activity, ICI therapy employs the patient's own immune system to perform the task of identifying and eliminating cancerous cells. The hope inherent in this concept is to more accurately identify the problematic cells and reduce the adverse effects associated with traditional chemotherapy, which result in the collateral deaths of many healthy cells. However, the intended effect of ICIs in promoting the activation and clonal expansion of T cells holds novel challenges for patient management. Given the novel approach that ICI therapy follows, the fundamental intended target of increasing the activity of the immune system presents an array of adverse effects that differ from traditional chemotherapy. T cells have the ability to infiltrate nearly all organs, and are therefore capable of causing adverse effects in nearly any bodily system [50]. Additionally, these effects can vary in appearance and in time from exposure to presentation, making them more difficult to detect and attribute to ICI therapy. A further challenge lies in the lack of identifiable intrinsic risk factors to guide suitable candidates for this therapy. The first-line therapy for managing immune-related adverse events (irAEs) involves systemic corticosteroids to dampen the overstimulated immune response, with the intention of reducing the adverse symptoms [50]. The manifestations of irAEs include a broad spectrum of rheumatologic conditions [50]. Among the more severe are drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, encephalitis, pneumonitis, hepatitis, and myocarditis [50]. It is important to maintain

awareness that novel approaches beget novel adverse effects, and irAEs may have a significant bearing on the evaluation of cost-effectiveness [50].

Concluding remarks

The increasing prevalence of HCC worldwide perpetuates the need for more effective therapy to combat this widespread and deadly cancer. Improvement in HCC treatment is likely to be accomplished through optimization of the tools at hand to identify biomarkers, refine combination therapy techniques, and expand to triple therapy regimens. Improved identification of significant biomarkers is required to achieve a more consistent therapeutic benefit in regimens containing ICI medications.

Advances in HCC therapy have been substantial in recent years, but it is important to reconsider the etiology of HCC. Interventions that mitigate risk factors contributing to the development of HCC should not be overlooked as part of a multifaceted approach. The optimal way to address the occurrences of HCC is through prevention of key risk factors that result in liver damage. Strategies to prevent chronic liver disease by addressing the implications of this dynamic epidemiologic environment may play an important role in HCC reduction.

Systemic therapy has seen many groundbreaking advances in the treatment of HCC over the last decade. Continuing developments are encouraging, as research continues towards unlocking the potential of ICI therapeutic interventions in treatment of HCC in a landscape of epidemiologic shift and rising numbers of cases around the world.

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