Immunotherapy in hepatocellular carcinoma: an overview of immune checkpoint inhibitors, drug resistance, and adverse effects

Abstract: Hepatocellular carcinoma (HCC) is a concerning liver cancer with rising incidence and mortality rates worldwide. The effectiveness of traditional therapies in managing advanced HCC is limited, necessitating the development of new therapeutic strategies. Immune checkpoint inhibitors (ICIs) have emerged as a promising strategy for HCC management. By preventing tumor cells from evading immune surveillance through immunological checkpoints, ICIs can restore the immune system’s ability to target and eliminate tumors. While ICIs show promise in enhancing the immune response against malignancies, challenges such as drug resistance and adverse reactions hinder their efficacy. To address these challenges, developing individualized ICI treatment strategies is critical. Combining targeted therapy and immunotherapy holds the potential for comprehensive therapeutic effects. Additionally, biomarker-based individualized ICI treatment strategies offer promise in predicting treatment response and guiding personalized patient care. Future research should explore emerging ICI treatment methods to optimize HCC immunotherapy. This review provides an overview of ICIs as a new treatment for HCC, demonstrating some success in promoting the tumor immune response. However, drug resistance and adverse reactions remain important considerations that must be addressed. As tailored treatment plans evolve, the prospect of immunotherapy for HCC is expected to grow, offering new opportunities for improved patient outcomes.

Keywords: hepatocellular carcinoma; liver cancer; immune checkpoint inhibitors; drug resistance; adverse effect; immunotherapy

Introduction

Background information

Hepatocellular carcinoma (HCC) ranks among the prevalent forms of malignant tumors, posing a serious health burden worldwide [1]. Despite the notable progress made in the domains of cancer prevention, screening, and therapy, the incidence and fatality rates linked with HCC continue to exhibit an upward trend [2], accounting for over 1 million deaths annually [3]. Each year, close to 600,000 fresh instances of HCC are documented globally, with more than half occurring in the Asia-Pacific region, where HCC is the most prevalent, and in tropical Africa [4, 5]. However, a recent survey in the United States suggests that the incidence of this disease may have peaked in the last few years [6, 7]. Furthermore, the prevalence of HCC has exhibited an upward trend in recent decades, notably in instances associated with chronic viral infections of hepatitis B and C [8].

HCC has the third-highest mortality rate after lung cancer [9]. A large percentage of patients are diagnosed at an advanced stage because most cases are difficult to detect in the early stages, restricting the effectiveness of treatments such as surgical resection and liver transplantation. Alpha-fetoprotein (AFP) and ultrasound are the main modalities for screening high-risk groups for HCC and early diagnosis of HCC, but both tests have their shortcomings. 30–40 % of HCC patients will have negative AFP and the lowest limit of resolution for ultrasound is 1 cm [10]. However, it is not advisable to utilize AFP alone (without hepatic ultrasound) as a surveillance test for HCC because of its reduced sensitivity and specificity in detecting HCC [11]. Additionally, ultrasound is less reliable in obese patients and those with nodular livers. Furthermore, individuals with HCC exhibit little clinical manifestations throughout the initial phases.
This has led to many HCCs being difficult to detect in the early stages, thus leading to the development of HCC and missing the best treatment period. In addition, the resistance of HCC to traditional radiotherapy and chemotherapy further complicates curative efforts. Currently, the primary therapeutic modalities for HCC include liver transplantation, radiation, local ablation, chemotherapy, and targeted therapy. However, these treatments present certain difficulties and restrictions [12–14].

Challenges and limitations of existing HCC treatments

The following are the major challenges and limitations:

Surgical resection

The surgical resection of HCC is widely acknowledged as the most important therapeutic approach, renowned for its remarkable efficacy. Notably, this intervention has demonstrated a post-resection 5-year survival rate that can ascend to 70% [15]. However, it is only suitable for early cases and individuals with a strong liver function reserve. Surgical resection is not feasible for most advanced cases. Patients must meet the following requirements to undergo surgical resection: Child-Pugh class A and ICG-R15 levels between 20 and 30% are typically regarded as prerequisites for surgical resection; additionally, patients with cirrhosis must have residual liver volumes that are greater than 40% of the standardized volumetric liver volume, or patients without cirrhosis must have residual liver volumes greater than 30% of the standardized volumetric liver volume.

Local ablation

Local ablation techniques, such as radiofrequency ablation (RFA) and microwave ablation, have made significant progress in the treatment of early-stage HCC [14, 16, 17]. RFA has been determined to be a more economically efficient option compared to surgery in the initial stages of treatment for individuals with a solitary nodule measuring less than 2 cm or two to three nodules equal to or smaller than 3 cm [18, 19]. RFA exhibited a greater incidence of necrosis in comparison to PEI [20–22]. However, their ability to effectively regulate tumor progression and metastasis to the liver has not yet been demonstrated. RFA is the most successful therapy for early-stage HCC. Nevertheless, a pathological investigation revealed that cancer cells persist after treatment and are vulnerable to recurrence [23].

Chemoradiotherapy

Traditional chemoradiotherapy has limited effectiveness in treating HCC, and drug resistance is widespread among patients. In addition, radiation therapy poses risks to patients with impaired liver function.

Targeted therapy

Several tyrosine kinases and angiogenesis inhibitors have been utilized in the therapeutic management of HCC. However, the efficacy of individualized, targeted therapies is frequently inadequate for effectively managing tumor progression, resulting in the emergence of drug resistance [24, 25].

Although there are several traditional treatment options available for HCC, the effectiveness of each strategy is insufficient. Furthermore, the limitations inherent in these methods prevent effective management of tumor recurrence and metastasis. Therefore, there is a need to explore new methods to control tumor recurrence and metastasis in addition to these treatment methods.

Emergence and application prospect of immune checkpoint inhibitors

The last several years have witnessed a significant breakthrough in cancer treatment with the emergence and application of immune checkpoint inhibitors (ICIs), ushering in a novel era in the field [26]. ICIs, represented by IgG monoclonal antibodies, block immunological checkpoint molecules such as cytotoxic T-lymphocyte cell-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death 1 ligand 1 (PD-L1) [27]. These proteins are of utmost importance in evading immune surveillance due to their capacity to restrict the response of CD8+ T cells. The co-expression of these proteins in both malignant cells and antigen-presenting cells (APCs) has considerable importance [28].

Immunotherapeutic agents known as ICIs have the ability to restore the immune system’s ability to target and eliminate tumors by inhibiting the costimulatory pathway that links these tumors to immune cells. ICIs have given patients with HCC new hope for effective treatment. Early clinical trial results showed that nivolumab (as an anti-PD-1 antibody) has shown encouraging efficacy in a subset of patients with HCC [29]; therefore, the U.S. Food and Drug Administration (FDA) accelerated the approval of nivolumab for advanced HCC in 2017 [30]. Additionally, because the therapeutic mechanism of ICIs differs from that of previous
medications, it may open new possibilities for the comprehensive treatment of HCC.

Although ICIs have shown significant therapeutic benefits in some patients, their efficacy remains limited. Furthermore, ICIs can induce adverse reactions, including immune-related toxicity. Hence, it is imperative to conduct research on the mechanisms underlying resistance to ICIs and adverse effects experienced by patients with HCC.

In conclusion, ICIs represent a novel therapeutic strategy with therapeutic potential for HCC. Therefore, this review focuses on providing an in-depth description of the therapeutic mechanism, drug resistance, and adverse reaction mechanisms of ICI. The aim is to better optimize the therapeutic regimen of ICIs combined with oncology immunotherapy (OI) and to provide more effective and safer therapeutic options for clinical patients.

Mechanism and role of ICI therapy in HCC

HCC is an aggressive neoplasm characterized by its propensity for invasion and metastasis. Conventional therapies, including radiation, chemotherapy, and surgical resection, often have limitations when treating HCC. However, in recent years, ICIs have garnered recognition as an optimal therapy modality for individuals diagnosed with HCC. ICI therapy is a novel immunotherapeutic approach that has the capacity to hinder tumor growth and metastasis by modulating the immunological micro-environment of the tumor and enhancing the immune response of the individual [31, 32].

Immune checkpoint and its biological function

The regulation of T-cell immune response is critically influenced by immunological checkpoints, such as PD-1 and CTLA-4.

PD-1, a type I transmembrane protein of 288 amino acids, is mostly expressed on the surface of APCs, dendritic cells (DCs), CD4+ T cells, CD8+ T cells, and other immune cells. It is a member of the CD28 superfamily.

PD-L1, also referred to as B7-H1, and PD-L2, known as B7-DC, are type I transmembrane proteins that belong to the CD274 superfamily. Recent studies confirmed that both PD-L1 and PD-L2 serve as ligands of PD-1 [33, 34]. Furthermore, both ligands are present on the surface of malignant cancer cells, with PD-L1 expressed at a higher level [35].

CTLA-4 and CD28 both belong to the IgSF family, which are highly homologous to each other, and their natural ligand is the B7 molecule. Therefore, competitive binding of the B7 molecule often occurs between CTLA-4 and CD28. The negative immunocompetence regulator, CTLA-4, is mostly expressed on regulatory T (Treg) cells, CD28; however, functions as a promoter of T cell proliferation [36–38].

T cells serve as the primary effector cells responsible for mediating cellular immunity. First, APCs are responsible for processing the captured antigens into antigenic peptides. These peptides establish binding interactions with major histocompatibility complex (MHC) class II molecules located on the surface of the APCs, resulting in the formation of an MHC-antigenic peptide complex. The complex’s association with the T-cell receptor (TCR) on primary T cells plays a crucial role in facilitating the transmission of the initial activation signal, thereby starting the process of T-cell activation. In addition, APCs express B7 molecules on their cellular membranes, which can bind to CD28 receptors located on T cells. This interaction between B7 molecules and CD28 receptors is crucial because it facilitates the provision of a secondary signal necessary for the activation of T cells. The presence of this dual signaling pathway enhances the process of T cell multiplication. Activated T cells increase the expression of CTLA-4 on their cellular membranes. CTLA-4 demonstrated a higher binding affinity towards the B7 molecule than CD28. When CTLA-4 binds to its ligand, it exerts a suppressive effect on T cells, hindering their excessive activation of T cells [39, 40].

The interaction between PD-L1 and PD-1 in tumor cells leads to the production of IL-10 [41], a molecule with negative immunomodulatory effects. Localized accumulation of this inhibitor within the tumor creates a strong immunosuppressive environment. Consequently, the function of the immune cells that infiltrate this zone is inhibited, enabling tumor cells to escape surveillance by the immune system.

Types of ICI drugs and how they work

ICIs are therapeutic antibody drugs that target specific immune checkpoints. This class primarily comprises PD-1 and CTLA-4 inhibitors. The underlying theoretical framework of PD-1/PD-L1 inhibitors, such as nivolumab and pembrolizumab, posits that by employing these inhibitors to interact with PD-1 receptors on T cells or PD-L1 receptors on tumor cells, it is possible to circumvent the immunosuppressive mechanisms responsible for tumor immune evasion. CTLA-4 inhibitors, especially ipilimumab, exhibit an affinity for the CTLA-4 molecule located on the exterior of stimulated T cells. Consequently, this interaction modulates
the active status of T cells and augments their capacity to effectively target and combat tumors [42, 43]. A deeper understanding and research on CTLA-4 suggest that anti-CTLA-4 antibodies may not function through immune checkpoints but rather play a therapeutic role by eliminating Tregs in tumor tissues [44, 45]. The mechanism of immune checkpoints and immune checkpoint inhibitors is illustrated in Figure 1.

The therapies in question involve the use of monoclonal antibodies that selectively target the receptors CTLA-4 and PD-1, as well as the ligand PD-L1. These receptors and ligands are known to play a vital role in the regulation of T cell activation. The activation of T cells necessitates the existence of two distinct signals. The initial signal involves the recognition of antigens by the TCR, subsequent to the presentation of antigens by MHC class II molecules on the surface of APCs. The second signaling pathway involves the modulation of signaling through the binding of CD80 or CD86 to the CD28 receptor. CTLA-4 is situated on the cellular membrane and engages in competitive interaction with the CD28 receptor to connect with CD80 or CD86, hence inhibiting T cell activation. CTLA-4 inhibitors obstruct the binding of CTLA-4 to either CD80 or CD86, thereby impeding T cell activation. The cell surface receptor known as PD-1 is present in T cells and can trigger death in T cells that are specific to antigens. It also has the capacity to prevent apoptosis in Treg cells. This effect is achieved through the receptor’s interaction with its ligand [46, 47]. The expression of PD-L1 is observed in both neoplastic and myeloid cell populations. This interaction plays a beneficial role in mitigating autoimmunity under normal physiological conditions. Cancer cells employ this strategy to evade immune surveillance by increasing the expression of PD-L1 [48, 49]. Inhibitors of PD-1 and PD-L1 impede the interactions between PD-1 and PD-L1, thereby promoting cell activation and viability.

Immunomodulatory effects of ICI drugs in HCC

The immunomodulatory effects of ICI therapy in HCC are mainly reflected in the following aspects:

Enhancement of anti-tumor effects

ICI drugs have the capacity to reinstate the suppressed functionality of T cells, enhance the cytotoxicity of T lymphocytes (CTLs) toward malignant cells, and facilitate immune-mediated eradication of tumors [50, 51]. The potential of immunotherapy lies in its ability to augment the immune response in humans through the inhibition of the PD-1/PD-L1 or CTLA-4 pathways. This disruption of the immune evasion strategies employed by cancer cells effectively impedes the suppression of T-cell function [52].
Changes in immune cell infiltration

The application of immune ICIs facilitates the recruitment of several populations of immune cells, such as CD8+ T cells, natural killer (NK) cells, and macrophages. It is well-established that M1-type macrophages enhance anti-tumor immunity. Currently, some scholars have found that the use of pembrolizumab and nivolumab in the treatment of advanced non-small cell lung cancer affects tumor-associated macrophage polarization and cytotoxic T cell activation. Moreover, both pembrolizumab and nivolumab up-regulate the ratio of M1 and the secretion of cytokines related to the M1 phenotype, such as IFN-γ, TNF-α, etc. [53, 54]. The augmentation of these immune cells can enhance the immunogenicity of tumors and optimize the immune equilibrium within the tumor microenvironment (TME).

Modulation of immune tolerance

ICI therapy can reanimate T cells inactivated by tumor escape in some patients with HCC and improve the immune tolerance of patients to tumor antigens. This mechanism has the potential to augment the patient’s immune response to tumor-associated antigens, thereby impeding tumor growth and metastasis.

Although ICI therapy has shown some efficacy in HCC treatment, it has some limitations and adverse reactions. Some patients have a low or no response to ICI, potentially due to the presence of tumor immune evasion mechanisms and immunosuppression inside TME. In addition, ICI may cause immune-related adverse reactions such as immune-mediated hepatitis, pneumonia, and gastrointestinal inflammation. Therefore, individualized evaluation and monitoring are required for the clinical application of ICI therapy to improve treatment safety and effectiveness.

In summary, ICI therapy has an important immunomodulatory effect on HCC, promoting tumor immune elimination and inhibiting tumor growth. However, additional research is necessary to acquire a more thorough comprehension of the mechanisms that underlie ICI therapy. This will allow for the refinement of treatment regimens aimed at improving treatment outcomes in patients with HCC.

Clinical trial and efficacy of ICI therapy in hepatocellular carcinoma

Summary of results from early clinical trials

ICIs have garnered significant interest in HCC management. Numerous clinical trials have assessed the effectiveness and safety of ICI therapy in patients diagnosed with HCC. The results of these trials provide a valuable point of reference for the utilization of ICIs in HCC management.

Initially, clinical trials evaluating the efficacy of specific ICIs, including the well-studied anti-PD-1 antibodies Nivolumab and Pembrolizumab, were conducted. Research results have demonstrated the efficacy of a single anti-PD-1 antibody treatment in a subset of patients with HCC. This treatment approach has resulted in substantial disease control and increased survival rates [29, 55]. Numerous studies have shown a strong association between the number of tumor mutations found in HCC patients’ tumors and how responsive those individuals were to anti-PD-1 antibodies afterward. In the current study, it was found that the combination of anti-PD1 and anti-VEGFR2 antibodies increased the level of infiltrating CD8+ T cells, and a higher degree of CD8+ T cell infiltration in tumor tissues tends to mean better survival [56]. Specifically, patients who exhibit a higher burden of mutations are more inclined to get favorable outcomes with ICI therapy [57].

Concurrent ICI usage has been studied in prior clinical trials. For example, anti-PD-1 antibodies have been used in conjunction with anti-CTLA-4 antibodies to enhance the anti-tumor effect of the immune system by simultaneously acting on different immune checkpoint pathways [58]. The IMbrave150 trial demonstrated a significant prolongation of overall survival in the atezolizumab + bevacizumab group compared to that of the sorafenib group; with the 6- and 12-month survival rates in the atezolizumab + bevacizumab group being 84.8 and 67.2 %; and 72.2 and 54.6 % in the sorafenib group, respectively. The progression-free survival (PFS) in the atezolizumab + bevacizumab group was significantly higher compared with that of the sorafenib group (median time, 6.8 vs. 4.3 months) [59]. The CheckMate 040 phase I and II clinical trials evaluated the efficacy of nivolumab in patients with or without prior sorafenib use in non-comparative studies. The results of the phase II trial demonstrated an overall response rate (ORR) of 20 %. Additionally, the median remission duration was found to be 9.9 months, with a 9-month survival rate of up to 74 % [29]. Furthermore, the treatment safety profile was deemed manageable.

Combination of ICI and conventional therapy

The use of ICI drugs alone may not be sufficient to address the varied needs of all individuals due to the complex nature and unpredictability of HCC, even if there have been some encouraging results shown in patients with HCC treated with ICI therapy. Therefore, researchers have attempted to
combine ICI with traditional treatment methods to achieve improved results.

A common strategy is to combine ICI with local treatments, such as resection, RFA [60, 61], transarterial chemoembolization (TACE) [62–65], stereotactic body radiotherapy (SBRT) [66], or embolization via microspheres loaded with yttrium-90 (Y-90) [67–69]. Enhancing the efficacy of ICIs in the treatment of HCC through localized treatments necessitates the consideration of an important concept, immunogenic cell death [70]. An important feature of immunogenic death is that cells release intracellular molecules, such as proteins, nucleic acids, etc. upon death. These molecules can be recognized by the body's immune system and induce a more intense immune response. According to this concept, radiotherapy or other physical treatments lead to destruction at the cellular level or tissue level, prompting the release of more antigenic substances, thus enhancing the therapeutic efficacy of ICIs [71]. A clinical trial involving 36 patients was used to assess the effectiveness of tremelimumab in combination with RFA or chemoablation. The trial results demonstrated that 5 patients (26.3%) achieved a definite partial response. Furthermore, a tumor biopsy performed during the sixth week demonstrated an augmentation of CD8+ T cells, suggesting a positive outcome in terms of clinical efficacy. The study observed progression-free survival rates of 57.1 and 33.1% at 6 and 12 months, respectively. In addition, the median time to tumor progression at 6 and 12 months was 7 and 4 months, respectively [72]. Several studies have revealed that when utilized to treat HCC, the combination of ICIs and TACE displays a favorable safety profile. Additionally, the utilization of this combined therapeutic approach has demonstrated notable enhancements in the duration of time during which patients remain PFS. There is a possibility that this therapy may lead to downstage HCC [73]. Preliminary results have shown that these combined strategies have achieved good therapeutic effects in some patients with HCC; however, the effectiveness and safety of the aforementioned treatments still need to be confirmed through additional clinical trials.

Combination of targeted therapy and immunotherapy

With the widespread use of ICI therapy in HCC, researchers have begun to explore the possibility of combining targeted drugs with immunotherapy. Targeted therapies are designed to selectively target specific mutations or activate signaling pathways within tumor cells, thereby inhibiting their growth or promoting cell death. In contrast, the primary objective of immunotherapy is to address neoplasms by activating the immune system to identify and initiate an assault on malignant cells. The combination of these two therapies is expected to provide a more effective anti-tumor strategy. The IMbrave150 trial showed that combination therapy is superior to monotherapy, especially targeted therapy combined with ICIs [59]. The combination of antiangiogenic therapy and ICIs for HCC has become the current mainstream targeted therapy combined with immunization [74–76].

Sorafenib is a commonly used targeted therapeutic agent and an oral multi-target, multikinase inhibitor with dual anti-tumor effects that inhibit tumor angiogenesis and suppress tumor cell production [77]. However, the efficacy of this treatment remains limited. Studies have shown that ICI therapy combined with sorafenib may exert synergistic effects and significantly improve the survival rates of patients with HCC. For example, the clinical trial IMbrave150 provided evidence that the simultaneous application of pembrolizumab, an anti-PD-1 antibody, and sorafenib led to a significant increase in both PFS and OS compared with the use of sorafenib alone [59]. The findings of this study suggest that the simultaneous use of targeted therapy and immunotherapy shows potential for improving the effectiveness of treatment in patients with HCC.

Combination with ICIs

In addition to the utilization of ICI as a monotherapy, scholars are currently exploring the potential of synergistic combinations including ICI and other immunotherapeutic agents. For example, the combined use of ICI and anti-CTLA-4 antibodies has shown synergistic effects in melanoma and other cancers and is the most effective combination, which increases the number of CD8+ T cells and the possibility that the immune system responds to cancer cells [78, 79]. Hence, investigating the potential of combining diverse immunotherapeutic drugs emerges as a promising avenue for addressing HCC treatment.

Therefore, clinical trials of CTLA-4 inhibitors in combination with PD-1/PD-L1 inhibitors for the treatment of HCC have emerged. The combination of tremelimumab and durvalumab is the first immunotherapy to simultaneously target PD-L1 and CTLA-4. This treatment has demonstrated success in a phase III clinical trial known as the HIMALAYA trial [80]. The trial consisted of four arms: Arm 1 received a single dose of tremelimumab (300 mg) combined with durvalumab (1,500 mg every 4 weeks) using the STRIDE regimen (T300 + D arm in Phase I/II trial). Arm 2 received durvalumab alone (1,500 mg every 4 weeks). Arm 3 received four doses of tremelimumab (75 mg every 4 weeks) combined with
durvalumab (1,500 mg every 4 weeks) (T75 + D). Arm 4 received sorafenib (400 mg twice daily). The trial results indicated that the STRIDE arm had a median overall survival (OS) of 16.43 months (95% CI: 14.16–19.58), while the sorafenib arm had a median OS of 13.77 months (95% CI: 12.25–16.13). The STRIDE regimen achieved an objective remission rate (ORR) of 20.1% (with a complete remission rate of 3.1%), while the durvalumab regimen had an ORR of 17.0% (CR rate of 1.5%). The disease control rates for the STRIDE regimen, durvalumab, and sorafenib were 60.1, 54.8, and 60.7%, respectively. The STRIDE regimen, durvalumab, and sorafenib had durations of response of 22.34, 16.82, and 18.43 months, respectively. Hence, it can be inferred that the STRIDE regimen surpasses single-agent durvalumab in terms of effectiveness and exhibits a safety profile that can be easily managed.

In conclusion, early clinical trial findings point to some benefits of ICI therapy in HCC, with some patients experiencing enduring disease control and extended survival. However, owing to the complexity and heterogeneity of HCC, the application of a single ICI drug cannot meet the needs of all patients; therefore, the combination strategy has become a research hotspot. OS, PFS, ORR, and durability of clinical response are common metrics for gauging the effectiveness of ICI therapy. However, additional clinical investigations are required to substantiate these findings and investigate more efficacious therapeutic approaches to enhance the treatment outcomes of individuals diagnosed with HCC.

**Mechanisms and pathways of drug resistance**

HCC is challenging to treat using anti-tumor therapy. The introduction of ICIs has presented novel therapeutic prospects for patients with HCC. However, some patients exhibit suboptimal responses to ICI therapy or develop resistance and adverse reactions. Therefore, understanding the mechanisms underlying resistance and adverse reactions associated with ICI therapy in HCC is of considerable importance.

**Mechanisms of primary treatment resistance**

Initial resistance to ICI therapy in HCC patients may involve multiple mechanisms.

First, the presence of unconventional immune checkpoint molecules on the extracellular surface of HCC cells has the potential to impede the efficacy of treatment interventions. The overexpression of PD-L1 on the cellular membrane of HCC cells may reduce the efficacy of ICI therapy. Additionally, other immunosuppressive factors in HCC cells, such as CTLA-4, TIM-3, and LAG-3, may participate in the development of drug resistance [81–83].

Secondly, the immune microenvironment of patients with HCC may affect ICI therapy [84]. HCC cells exhibit high immune tolerance. TME harbors a substantial number of immunosuppressive cells and molecules, including Treg cells and the inhibitory enzyme indoleamine-2,3-dioxygenase (IDO). These factors have been identified as contributors to the compromised immune response observed in HCC patients, thereby reducing the efficacy of ICI therapy [85–87].

Finally, there are multiple immune escape mechanisms in the microenvironment of patients with HCC that may lead to initial drug resistance. HCC cells evade immune response by reducing antigen presentation and increasing the expression of signals that facilitate immune evasion. In addition, HCC cells can escape immune detection by promoting the selective proliferation of immune cells, leading to compromised immune cell efficacy and the release of immunosuppressive substances.

**Effect of gene variation on ICI treatment**

Genetic variation is a significant contributing factor to the variability observed in response to ICIs in patients with HCC. Recent research suggests that specific genetic alterations have the potential to influence the responsiveness and resilience of HCC cells towards ICIs. For example, mutations commonly found in HCC patients, such as TP53, CTNNB1, and AXIN1, may be related to the effectiveness of ICI therapy [88]. Mutations in TP53 can lead to the immune escape of HCC cells, thus reducing the efficacy of ICI therapy. In addition, mutations in CTNNB1 and AXIN1 may alter the activity of the Wnt/β-catenin signaling pathway [89, 90], thereby affecting the sensitivity of HCC cells to ICI therapy.

The existence of a link between the gene expression signature associated with T-cell infiltration and the efficacy of immune checkpoint blockade has been revealed [91]. Furthermore, the association between the Wnt/β-catenin pathway and insufficient T-cell infiltration in tumors has been frequently documented [92, 93]. AXIN1 and CTNNB1 are recognized as key regulators in triggering of the Wnt/β-catenin pathway. Notably, it has been demonstrated that in patients with HCC, there is a decrease in AXIN1 expression. Consequently, this leads to the stimulation of the Wnt/β-catenin pathway [89]. In a previous investigation, it was
observed that CTNNB1 exhibits a correlation with the process of phosphorylation and subsequent degradation of β-catenin. Plausibly, CTNNB1 is considered a potential biomarker for prognosticating resistance to ICI [94]. The TP53 gene, as a prevalent class of genes with pro-carcinogenic properties, exhibits a robust association with the occurrence of tumors, particularly in cases where mutations are present. A recent scholarly investigation has revealed that mutations occurring in the TP53 gene have the capacity to impede both cell-autonomous and cell-non-autonomous signals [95–98]. Furthermore, these mutations have been identified as having a counteractive effect on innate immune pathways, leading to the evasion of immune responses against tumors. Consequently, the effectiveness of ICIs is significantly impacted by these mutations. However, it is crucial to conduct further comprehensive research to fully elucidate the precise mechanisms that underpin these occurrences.

Similarly, mutations in immune-related genes may affect the response to ICI therapy. For example, interferon (IFN) is associated with the efficacy of ICI therapy and mutant alleles may be associated with survival and treatment responses [99]. The efficacy of ICIs is impacted by the influence of IFN on T-cell exhaustion. This is achieved through the upregulation of PD-L1 expression, together with the potential induction of other inhibitory ligands, including herpesvirus entry mediator, among others [100]. Further, a supplementary inquiry has discovered that IFN-γ plays a role in promoting T-cell fatigue by interacting with PD-L1. Moreover, it has been observed that the reciprocal antagonism of IFN signaling in both cancer cells and immune cells engenders a constrictive association between adaptive and innate immunity, thereby exerting an influence on the effectiveness of ICIs [101].

In summary, clinicians should conduct genetic testing in patients with a specific focus on TP53, CTNNB1, and AXIN1 prior to administering ICIs. This approach aims to ascertain the efficacy of ICIs in individual patients.

**Mechanism of tumor immune escape and drug resistance**

The tumor immune escape mechanism is an important factor that leads to drug resistance. HCC cells evade the host immune system via multiple pathways, thereby limiting the efficacy of ICI therapy.

An important immune escape mechanism is the increase in immunosuppressive cells such as Tregs and Myeloid-Derived Suppressor Cells (MDSCs) in HCC cells. MDSCs are generated from precursor myeloid cells in an immature or progenitor state and possess a notable capacity for immunosuppression [102]. Its mechanism of action involves the release of cytokines, specifically TGF-β1 and IL-10. Elevated IL-10 levels promote macrophage polarization towards the M2 phenotype, resulting in the decreased expression of MHC class II molecules in macrophages [103, 104]. Additionally, MDSCs stimulate the expansion of Tregs, leading to the reduced effectiveness of ICI therapy [105–107].

HCC cells have the capability to avoid immune responses through the upregulation of chemicals that exhibit immunosuppressive qualities. The immune-suppressive molecules PD-L1 and PD-L2 are frequently shown to interact with PD-1 receptors located on the surface of tumor cells, hence impeding the functionality of activated T lymphocytes. Researchers have shown that PD-L1 over-expression in HCC cells is related with ICI therapy resistance [108, 109].

In conclusion, understanding the underlying mechanisms of resistance and adverse reactions associated with ICI therapy in HCC is of the utmost significance for informing clinical practice and identifying novel therapeutic approaches. Through additional investigation, advances in addressing resistance mechanisms and optimizing ICI therapy will offer enhanced and secure treatment alternatives for patients diagnosed with HCC.

**Adverse effects of ICI therapy in HCC**

**Overview of common adverse reactions during clinical trials**

In clinical trials, ICI treatment has been shown to cause a series of adverse reactions in patients with HCC. The side effects of ICI therapy often appear as immune-related adverse events (irAEs), and the stimulation of the immune system plays a key role in their causation [110].

irAEs have the potential to manifest in several bodily systems and often emerge within a timeframe of 2–16 weeks following the commencement of treatment, with the specific duration contingent upon the particular system affected. Immune-related adverse events are usually categorized as early (<2 months) or late (>2 months), depending on the onset of illness. The early phase is usually characterized by dermal, gastrointestinal, or hepatotoxicity, whereas the late phase is often characterized by nephrotoxicity, pulmonary toxicity, or endocrine toxicity. The organs that are commonly impacted by irAEs are the skin, gastrointestinal tract, liver, endocrine system, lungs, and neurological system [111, 112].
Immune-related skin reactions include rash, itching, and dryness, and more severe reactions may lead to exfoliative dermatitis [113–115]. Gastrointestinal reactions include symptoms such as diarrhea, nausea, vomiting, and decreased appetite [116, 117]. Hepatic reactions often manifest as elevated liver enzymes and jaundice [118–121]. The most common endocrine reaction is thyroid dysfunction, which includes hyperthyroidism and hypothyroidism [122, 123]. Pulmonary reactions can lead to coughing, shortness of breath, and interstitial lung disease [124]. Reactions in the nervous system include peripheral neuritis and autoimmune encephalitis [125]. Additionally, there has been a suggestion that the concurrent use of ICIs may increase the likelihood of experiencing liver-related adverse effects compared to the use of ICIs alone [126, 127]. Hence, surveillance and administration of irAEs constitute crucial components in the management of patients receiving ICIs. Furthermore, the key outcome measure in most clinical studies is the incidence of irAEs.

Generally, the type of irAEs may not be specific to the type of cancer in which it occurs [128]. Nevertheless, a study revealed that individuals diagnosed with melanoma demonstrated a greater inclination to have skin-related irAEs in comparison to patients with non-small cell lung cancer and renal cell carcinoma who received PD-1 inhibitors as treatment [117]. This discrepancy in irAE occurrence could potentially be attributed to variations in the tumor microenvironment.

ICI treatment-related hepatotoxicity

There is a strong association between ICI treatment and hepatotoxicity. Hepatotoxicity is the result of an immune response triggered by ICI treatment and is characterized by increased liver enzyme levels and impaired liver function. Hepatic toxicity associated with ICI treatment typically occurs within weeks or months of treatment initiation [55, 118–121, 129].

ICI-induced by ICI treatment occurs primarily through a T cell-mediated mechanism [130]. ICI treatment can enhance T cell activation and function but may also trigger an autoimmune response, leading to hepatocyte damage. This reaction is known as immune-mediated hepatitis (IMH). Clinical features of IMH include elevated alanine aminotransferase and aspartate aminotransferase, jaundice, and abnormal liver function. In severe cases, ICI can cause liver failure [131].

Early diagnosis and intervention are important in ICI treatment-related hepatotoxicity. Clinically, monitoring liver enzyme levels and liver function is necessary, and detecting hepatotoxicity before or early in the onset of symptoms helps mitigate adverse reactions in patients. Mild IMH is usually managed with the discontinuation of corticosteroids and other immunomodulators. For severe hepatotoxic reactions, more aggressive treatment strategies, such as high-dose corticosteroids or anti-CD 20 monoclonal antibodies, may be required [111].

Other important adverse reactions and their management strategies

In addition to immune-related adverse effects and hepatotoxicity, ICI treatment is also associated with other important adverse effects. The following are some common adverse reactions and their management strategies:

Hematological abnormalities

The conditions encompassed within this category are anemia, thrombocytopenia, and leukopenia [119]. In cases of anemia and thrombocytopenia, the administration of blood transfusions or the utilization of growth factors may be necessary to ameliorate the patient's condition.

Cardiotoxicity

ICI treatment may cause myocarditis and cardiac dysfunction. For patients with cardiac-related symptoms, ECG monitoring and cardiac ultrasound may be required, and discontinuation or other treatment measures may be considered [132, 133].

Pulmonary toxicity

This includes pneumonia and interstitial lung diseases. If pulmonary toxicity is severe, ICI therapy may need to be stopped and hormone therapy or other immunosuppressive treatments may be necessary [134, 135].

Nephrotoxicity

ICI treatment may impair renal function. ICI therapy may be reduced or discontinued in patients with abnormal renal function. Owing to the extended half-life of ICI, it is imperative for clinicians to diligently monitor and assess a patient's condition [136, 137].

Individualized treatment strategies are important for managing the adverse effects of ICI therapy. It is imperative for clinicians to diligently observe patients for any untoward reactions, promptly intervene, and make informed decisions.
regarding treatment options to mitigate the negative consequences of adverse reactions and ensure the safety and efficacy of the treatment.

Although ICI therapy has shown significant potential for the treatment of HCC, the mechanisms of resistance and adverse reactions associated with ICI therapy should also be addressed. Understanding the occurrence and management of these mechanisms and reactions is critical for the effective application of ICI therapy in clinical practice.

Development prospect of individualized ICI treatment strategy

Biomarker-based individualized ICI treatment strategy

Researchers are looking for reliable biomarkers to develop individualized treatment strategies to better predict patient responses to and the adverse effects of ICI therapy. Biomarkers have the potential to facilitate the identification of individuals who are more likely to exhibit a favorable response to ICI drugs, as well as forecast the likelihood of experiencing adverse effects.

Several potential biomarkers have been proposed and validated for HCC. Prior research has established a notable correlation between tumor mutational burden (TMB) and the expression of PD-L1 in relation to the efficacy of ICI therapy in various cancer types [138, 139]. According to research, people with HCC who have high TMB levels might respond to ICI therapy more readily [139]. Furthermore, it is important considering the association between the response to ICI treatment and the degree of infiltration by immune cells, together with the expression of immune-related genes and proteins in tumor tissues [140, 141].

Based on these biomarkers, researchers are developing strategies to personalize ICI therapy. These markers facilitate the identification of patients who are more likely to have favorable responses to ICI drugs. This identification process enables the provision of more precise treatment alternatives and prognosis evaluations for these patients.

Emerging treatment methods and research directions of ICI

In addition to the traditional ICI treatment methods, some emerging ICI treatment methods and research directions have been actively explored. Several clinical trials are now being done to examine the possibility of ICI combination therapy to increase the efficacy of ICIs and enhance patient clinical outcomes [29, 59, 142]. Some studies have also shown that combination therapy with ICIs can change the immune microenvironment of tumors, increase the immune-presenting ability of antigens, and weaken the function of immunosuppressive cells, thereby increasing the sensitivity to ICIs and reducing their resistance [143, 144]. These methods may improve the efficacy and safety of ICI treatment.

Intestinal microbiota and ICI therapy

The significance of intestinal microbiota in the context of immunotherapy is noteworthy [145]. Recent research has indicated a potential association between the nature of gut microbiota and the efficacy of ICI therapy in patients. Therefore, modulation of the gut microbiota may be a strategy for improving the efficacy of ICI therapy [146]. More in-depth prospective and detailed studies on gut-associated flora are needed to gain insights into the efficacy of antibiotics on ICIs and the relationship between gut-associated flora and ICI efficacy.

Development of novel ICI

In addition to already marketed PD-1 and PD-L1 antibodies, researchers are working to develop novel ICI. For example, inhibitors such as LAG-3 and TIM-3 have been investigated and may expand the application of ICI therapy in HCC.

In conclusion, the development of individualized ICI strategies is important for HCC immunotherapy. The integration of targeted therapy and immunotherapy, personalized treatment approaches guided by biomarkers, the emergence of ICIs, and ongoing research endeavors are anticipated to offer enhanced and tailored therapeutic alternatives for individuals diagnosed with HCC. However, more studies and clinical trials are required to confirm the security and efficacy of these treatments, consequently giving medical professionals more thorough direction.

Advantages and disadvantages of individualized ICI therapy

Individualized ICI therapy in HCC is a promising approach, with studies showing positive outcomes in both advanced and early/intermediate stages of the disease [147, 148]. In a theoretical framework, it can be posited that the customized amalgamation of pharmaceutical agents tailored to the
specific condition of the patient confers a greater degree of benefit compared to the administration of a solitary drug. This advantage is manifested through the reduction of cytotoxicity and the optimization of the efficacy of inducing cellular demise. Furthermore, it is worth noting that the intricate mechanism of action exhibited by ICI drugs presents a significant opportunity for the utilization of combined conventional therapies as well as other targeted drug therapies. The utilization of combination therapy has been observed to augment the immunogenicity of tumors, thereby facilitating the infiltration of immune cells [149]. This transformative effect is particularly notable in tumors that initially exhibit insensitivity to ICI, as it renders them susceptible to therapeutic intervention. Additionally, combination therapy has been found to effectively mitigate drug resistance, broaden the range of applicability of ICI, and ultimately enhance the overall efficacy of ICI treatment. In a clinical investigation encompassing a cohort of 25 individuals, the utilization of SBRT in conjunction with sintilizumab [150, 151] was evaluated. The main purpose of this research was to assess the overall remission rate among patients, as indicated by mRECIST. The findings revealed a noteworthy remission rate of 96%, with 18 cases demonstrating complete remission and six cases exhibiting partial remission. Furthermore, the patients’ PFS at the 6-month mark was observed to be 96%, whereas the PFS at the 1-year mark reached 70%. Importantly, no unforeseen toxic reactions were documented during this investigation. Simultaneously, ICI neoadjuvant therapy can serve as an individualized treatment, seen as a method to reduce the extent of early or locally progressed disease. It can stimulate the body’s immune response against the tumor and enhance the results of surgery and cancer treatment [152]. It has been suggested that neoadjuvant use of checkpoint inhibitors may be superior to adjuvant therapy, and in a clinical study using ipilimumab and nivolumab as adjuvant therapy to improve outcomes in patients with stage III melanoma, 7/9 (78%) patients in the neoadjuvant group achieved pathological remission, with 3 patients in pathological complete responses (pCR), 3 approaching a pCR, and 1 patient achieving a pathological partial remission [153]. Nevertheless, recent reports indicate a greater occurrence of irAEs in combination therapy with ICIs compared to monotherapy with ICIs [154]. Furthermore, the incidence of irAEs was shown to be highest and at a significant level in patients receiving combination therapy [155]. Given this phenomenon, it is imperative that we thoroughly evaluate the selection of personalized therapy in our clinical practice, taking into account the advantages of personalized treatment as well as the elevated occurrence of immune-related adverse events resulting from combination therapy. Currently, there is a dearth of clinical trials focused on personalized treatment. It is our expectation that in the next few years, more researchers will shift their focus towards investigating this approach. In this way, medical practitioners will have the ability to select the suitable individualized ICI therapy for their patients, thereby diminishing patient resistance, averting severe irAEs, and enhancing the patients’ overall response to personalized treatment.

### Multi-parameter cascade therapy model applied to ICI treatment

Some scholars have proposed a new concept for HCC treatment called the multi-parameter treatment hierarchy model [156], which is mainly dedicated to going beyond the traditional stage-based treatment algorithms to provide a more personalized treatment decision-making framework. The model emphasizes the need for treatment decisions to go beyond single clinical indicators and to consider all aspects of the patient’s condition, and with the increasing number and complexity of therapeutic options, this multiparameter treatment decision-making model will show its value and necessity. In the multiparameter treatment hierarchy model, the multidisciplinary team plays a central role, which not only optimizes the treatment plan for individual patients, but also improves the overall quality of treatment decisions, forming the basis for the provision of high-quality, personalized healthcare services. Using this model, a more refined and personalized framework for treatment decision-making can be provided to HCC patients. If we use the multiparameter treatment hierarchy model for the personalization of ICI, we can further strengthen the personalization of treatment and optimize patient outcomes.

The utilization of individualized combination therapy involving ICIs exhibits promising merits. However, it is imperative to note the absence of a universally established, standardized, and individualized ICI treatment regimen. This undeniable reality inevitably amplifies the burden and complexity faced by medical practitioners. Furthermore, the pursuit of individualized treatment encounters certain obstacles. In light of the aforementioned considerations regarding the selection of pharmaceutical agents and the dosage of radiotherapy, it is imperative to acknowledge that the utilization of combination therapy may engender an augmented occurrence of irAEs. This phenomenon prompts a series of inquiries that necessitate expeditious elucidation. Specifically, it becomes imperative to ascertain whether the manifestation of irAEs is contingent upon the dosage administered or not. Furthermore, it is imperative to acknowledge that the implementation of personalized ICI
therapy will inevitably contribute to the increased financial strain experienced by patients. This is primarily due to the necessity of undergoing various diagnostic procedures, including genetic testing, immunohistochemistry, and imaging tests. Thirdly, it is imperative to acknowledge the dearth of dependable biomarkers in the context of immunotherapy with ICI. Despite concerted efforts to identify biomarkers that are indicative of response to ICI therapy, the current body of knowledge remains deficient in stable and reliable prognosticators. This inherent limitation significantly curtails the practicability and precision of implementing personalized treatment approaches.

**Current & future developments**

The current state of ICI therapy for HCC is characterized by ongoing developments encompassing numerous potential avenues of research and promising prospects.

First, further investigations should be conducted to explore the mechanisms underlying ICI therapy in HCC. Acquiring a full comprehension of the effects of ICI therapy on the immune evasion mechanisms utilized by tumors would significantly augment the progress of pioneering therapeutic approaches. Furthermore, the potential synergistic effects of combining ICI therapy with adjunctive treatments, such as chemotherapy and radiotherapy, warrant investigation to enhance the overall therapeutic efficacy.

Second, a complete clinical database should be established to accumulate additional clinical data on ICI treatment. The efficacy and safety of ICI therapy can be further verified through observational studies in large patient cohorts and more powerful evidence can be provided for the formulation of individualized ICI treatment strategies.

Moreover, it is crucial to undertake more clinical trials in order to examine the possible application of ICIs in certain subsets of patients. The utilization of ICI therapy in patients diagnosed with various subtypes of HCC enables the assessment of differential responses to ICI therapy among patients with distinct subtypes as well as the investigation of novel therapeutic targets.

This article presents a thorough examination of the efficacy, occurrence of irAEs, underlying mechanisms, and current status of employing ICIs as a therapeutic strategy for patients with HCC. In addition, we outline the methodology, benefits, and drawbacks of ICIs in the context of tumor therapy. As stated earlier, the treatment of HCC with ICI encounters certain obstacles; nevertheless, their potential for implementation remains high. Hence, it is imperative to enhance our understanding of tumor immunity as an initial step in investigating the TME and mechanisms underlying immune tolerance in HCC. This knowledge will facilitate the translation of research findings into practical outcomes, thereby informing the clinical applications of therapeutic drugs. Simultaneously, it is imperative to further elucidate the optimal timing of medication administration and the selection of combination regimens to personalize the medication. This is crucial because the establishment of an individualized ICI treatment strategy is pivotal for enhancing therapeutic efficacy and mitigating adverse reactions. Future research should prioritize the advancement of knowledge regarding the underlying mechanisms of ICI therapy. Efforts ought to be focused on the identification and validation of supplementary predictive biomarkers. Furthermore, the creation of a comprehensive clinical database is crucial in order to better the optimization of ICI treatment regimens and ultimately optimize the therapeutic results for patients diagnosed with HCC.

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