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Combined Treatment of HCC with CTLA-4 Inhibitors and PD-1/PD-L1 Inhibitors: Mechanisms, Progress and Challenges

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Abstract: HCC seriously threatens human health, and the treatment methods are of crucial importance. The tumor microenvironment is critical to the origin and progression of HCC, and aberrant regulation of the immune checkpoint signaling pathway is a key method by which tumor cells avoid immune surveillance. Conventional single-treatment approaches for HCC have drawbacks. Inhibitors of PD-1/PD-L1 and CTLA-4, together known as the "golden combination," are the primary treatment for primary HCC. Compared with single treatment, it has a synergistic effect and benefits in boosting the immune response against the tumor and growing the number of recipients. However, it also has challenges. This study examines the state of combination treatment in HCC clinical trials as well as the current understanding of immune checkpoint inhibitors. By elaborating the cancer immune mechanism, it examines the mechanisms of action of the CTLA-4 and PD-1/PD-L1 immune checkpoints, and also the theoretical underpinnings and synergistic mechanism of combination treatment in HCC. Together with clinical study data, it assesses the effectiveness and potential of combination treatment for the cure of HCC, thoroughly examines the effects of conjunction treatment of CTLA-4 inhibitors and PD-1/PD-L1 inhibitors in the immunologic therapy of HCC, and anticipates the future of combination treatment, offering useful references for HCC immunotherapy.

Keywords: Immune checkpoints (ICs), PD-1/PD-L1 inhibitors, hepatocellular carcinoma (HCC), CTLA-4 inhibitors, combined treatment.

1. Introduction

Hepatocellular carcinoma (HCC) is among one of the most common malignancies. The immune checkpoint (ICs) pathway in the tumor microenvironment (TME) has a complex regulatory mechanism that is essential to the development and occurrence of HCC. Immunotherapy is also important in the treatment of HCC. One of the key ways that tumor cells evade immune surveillance is through abnormal regulation of the ICs pathway. Due to the existence of the immune evasion mechanism, tumor cells can avoid immune detection and thus remain uncleared. Studying this issue can effectively address the problems of the judgment, detection and treatment direction of HCC cells. As of right now, it is understood that increasing the expression of ICs molecules (such as PD-1, PD-

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L1, CTLA-4, etc.) in the TME can prevent T cells from acting, which enables tumor cells to avoid the immune system's onslaught.

Both PD-1/PD-L1 inhibitors and CTLA-4 inhibitors have achieved certain therapeutic effects in the treatment of HCC, but the response rate of monotherapy is relatively low. A growing number of studies have concentrated on the application of combined treatment with them in hepatocellular carcinoma (HCC) since earlier reported clinical studies.The combined treatment is based on the theory that the two inhibitors can work in concert to improve the immune system's capacity to combat tumor cells. These inhibitors have demonstrated impressive therapeutic outcomes in the treatment of a variety of malignancies. The mechanism of action and effectiveness of the combination treatment in the treatment of HCC are still largely unknown, though, and there are certain possible hazards (such a higher risk of immune-related adverse events) and challenges.

The goal of this study is to gain a better understanding of the immune evasion mechanism of HCC by deeply examining the regulatory mechanism of ICs pathways in the TME, as well as the benefits and drawbacks of treating HCC with a combination of these two inhibitors. This will provide a theoretical foundation for the development of more effective immunotherapy strategies.

In conclusion, clarifying the pathogenesis of HCC, thoroughly exploring the regulatory mechanism of ICs pathways, and comprehending how the immunotherapy of HCC is affected by the combination of these two inhibitors is crucial for boosting the disease's therapeutic effect and patient prognosis.

2. The immune checkpoint pathways in the TME and HCC

2.1. The cancer-immune cycle

The cancer-immune cycle includes the following steps: release of tumor antigens, antigen presentation, T cell activation, migration of T cells to the cancerous tissue, recognizing cancer cells by T cells, and killing of tumor cells (Figure 1). When the immune system recognizes the antigens on the surface of tumor cells, it activates T cells, allowing them to migrate to the tumor tissue and carry out the function of killing tumor cells. The immune system can identify and eliminate emerging "non-self" components, including tumor cells.

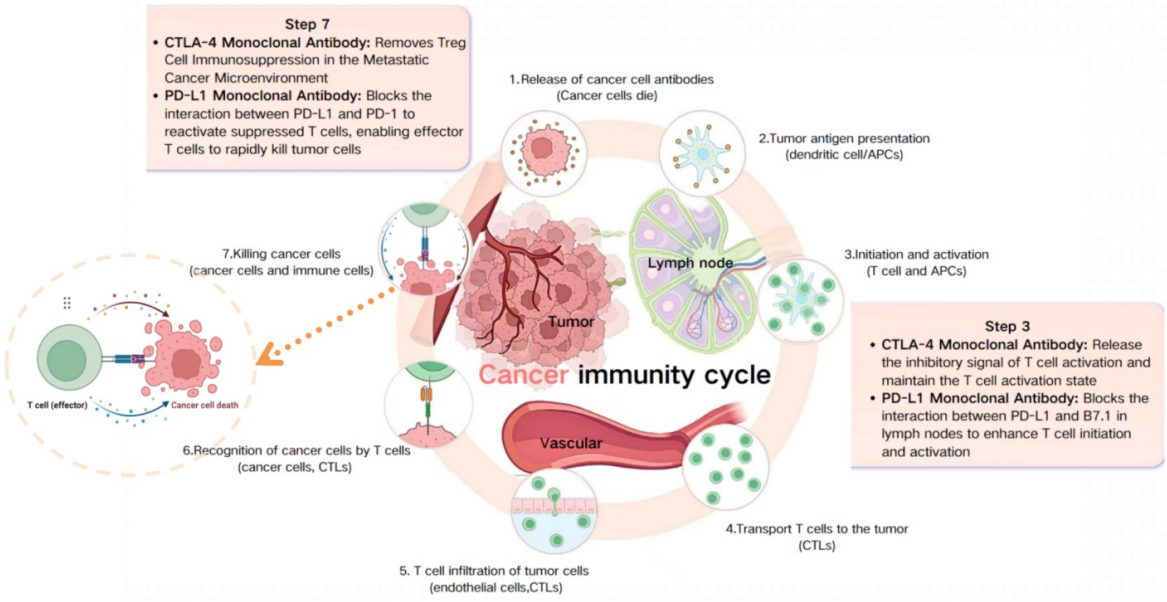


Figure 1: The Cancer-Immune Cycle

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Molecules of MHC on the surface of antigen-presenting cells (APCs) can attach to tumor antigens. These cells move to lymph nodes and transmit antigens to immature T cell receptors (TCR). The activation of antigens (the first signal) is not the exclusive source of the other co-stimulatory signals for T cells. The B7 family (CD80/B7-1, CD86/B7-2) on the external surface of APC and CD28 on the surface of T cells combine to create the second signal. During this process, By activating IL-2 secreted by CD4+ T cells, MHC class II molecules facilitate the proliferation and differentiation of CD8+ T cells into CTLs.The activated T lymphocytes flow along the blood to the tumor and invade it. When TCRs in the tumor tissue recognize the tumor antigens displayed by MHC molecules on the surface of tumor cells, they trigger T cells to release granzyme, perforin, and other substances that kill the tumor cells. Additionally, APC can move to lymph nodes to further activate CD8+ T cells after identifying tumor antigens. The cyclic immune cycle of tumors is this [1].

2.2. The mechanism of action of ICs

ICs are a regulatory mechanism in the immune system that has a significant regulatory function in the immune system. Within TME by inhibiting the activity of T cells to prevent excessive activation of the immune system. Among them, ICs proteins such as PD-1 and CTLA-4 play important roles in the process of T cell activation: during tumor immunization, the highly expressed these two ligands on the surface of tumor cells activate ICs and the ICs pathways, transmitting signals to immune cells, making them unable to effectively kill tumor cells. Therefore, the function of ICs inhibitors currently used in clinical practice is to enable immune cells to kill tumor cells.

2.2.1. PD-1/PD-L1 Pathway

PD-1 is a significant immune-suppressive molecule that is primarily expressed on the surface of activated T cells. By binding to its two ligands, it with PD-L2, which are expressed by tumor cells to evade immune elimination [2]. PD-L1 is a membrane-bound ligand of PD-1 and is highly expressed on the surface of tumor cells. When PD-1 binds to PD-L1, it promotes the phosphorylation of tyrosine in the immunoreceptor tyrosine-based switch motif (ITSM) domain of PD-1, which in turn causes the dephosphorylation of downstream protein kinases Syk and PI3K, suppresses the activation of downstream pathways (AKT, ERK, and so on), eventually inhibiting the transcription and translation of genes and cytokines essential for T cell activation, hence negatively regulating T cell activity.
PD-L1 monoclonal antibodies improve T cell priming and activation by inhibiting the interaction between itself with B7-1 molecules in lymph nodes. During the effector stage, its monoclonal antibodies disrupt the interaction between PD-L1 and PD-1, reactivating suppressed T cells and allowing the "resurrected" effector T cells (Te) to rapidly kill cancer cells [3].

2.2.2. CTLA-4 Pathway

The CTLA-4 gene encodes a transmembrane protein known as CD152, which is expressed on activated CD4+ and CD8+ T lymphocytes.CTLA-4 shares gene structure, chromosomal location, sequence homology, and expression of genes with the co-stimulatory molecule receptor (CD28) on the surface of T cells, and it additionally can bind to the co-stimulatory molecules (B7) on the surface of antigen-presenting cells. After binding to B7 molecules, It serves as a competitive ligand through its extracellular domain, occupying the B7 ligand of APCs and preventing CD28 signals, or it mediates a negative signal through its intracellular domain, suppressing T cell activation [4].

CTLA-4 monoclonal antibodies can help T cells stay activated throughout the activation stage by blocking signals that suppress T cell activation. During the effector stage, its monoclonal antibodies ease immunosuppression of regulatory T cells (Tregs) in the TME [5].

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2.3. The influence of TME on ICs pathways

TME has a crucial impact on the occurrence and progression of cancers, immune evasion, and ICs pathways. Tumor cells in the TME regulate ICs pathways by upregulating ICs ligands and secreting immunosuppressive factors to circumvent immune surveillance and promote tumor occurrence and development.

2.3.1. Tumor cells upregulate ICs ligands

By suppressing the activation, proliferation, and cytokine release of T cells, tumor cells upregulate ligands such as PD-L1, enabling tumor cells to evade the attack of the immune system. This is one of the major techniques for them to elude immune monitoring. For instance, research on ovarian cancer tumor cells has demonstrated that PD-L1 on their surface binds to PD-1 on T cells, preventing T cell activity and enabling tumor cells to evade the immune system. This prevents the immune system from recognizing and attacking tumor cells [6].

2.3.2. Immunosuppressive factors and Ics

ICs are also significantly influenced by immunosuppressive factors derived from tumor cells. TGF-β and IL-10 are immunosuppressive molecules in the TME that may raise PD-L1 expression, allowing tumor cells to evade the immune system.

Furthermore, certain extracellular vesicles, such as those containing miR-424, can be secreted by tumor cells and absorbed by immune cells that have infiltrated the TME. This can lead to a reduction in CD28 and CD80 expression in T cells and dendritic cells (DCs), which disrupts the transmission of T cell co-stimulatory signals. This prevents T cells from being fully activated to produce an anti-tumor response and results in patient resistance to immunotherapy [7].

2.4. Analysis of HCC and Related Pathways

In the process of the occurrence and development of HCC, numerous pathways are involved (Table 1) [8].

Table 1: Signal Pathways Related to HCC and Potential Molecular Targets

Signal Pathway	Potential Targets	Mechanism of Action in HCC	References
VEGF/VEGFR,PDGF/PDGFR,FGF/FGFR	VEGF,VEGFR,PDGFR,FGFR	Angiogenesis and the maintenance of mature blood vessels	[9,10]
IGF/IGFR	IGFR	Inhibition of cell proliferation, movement and apoptosis	[5]
HGF/c-Met	c-Met	The processes of tumor growth, invasion and angiogenesis	[11]
PI3K/AKT/mTOR	AKT, mTOR	Cell proliferation, regulation of cell cycle, and anti-apoptosis	[12]
RAS/RAF/MEK/ERK	RAF, MEK	Cell growth, survival and regulation of cell differentiation	[13]
JAK/STAT	STAT	Cell differentiation, proliferation, apoptosis	[5,14]

VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Factor Receptor; PDGF: Platelet-Derived Growth Factor; PDGFR: Platelet-Derived Growth Factor Receptor; FGF: Fibroblast Growth Factor; FGFR: Fibroblast Growth Factor Receptor; IGF: Insulin-Like Growth Factor; IGFR: Insulin-Like Growth Factor Receptor; HGF: Hepatocyte Growth Factor; c-Met: Hepatocyte Growth Factor Receptor.

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The occurrence of HCC stems from the alteration and gradual accumulation of the initial and cancer-initiating genomes in the body, inducing factors can prompt autonomous or non-autonomous changes in tumor cells, such as cell proliferation, survival, invasion, and the development of immune tolerance, at various stages of tumor development, including the initiation stage, progression stage, metastasis stage, and when resistance to treatment emerges. It can thus be seen that the formation of tumors results from a unique combination of genetic alterations and epigenetic modifications. These findings fully demonstrate the complexity and variability in the occurrence and development of HCC. Since congenital factors are difficult to avoid, the treatment of HCC should focus on aspects such as immunotherapy.

3. The therapeutic mechanisms of CTLA - 4 inhibitors and PD - 1/PD - L1 inhibitors respectively

3.1. The mechanism of action of CTLA - 4 inhibitors

In the immunotherapy of HCC, CTLA-4 antibodies, a significant kind of ICs inhibitors, are essential. Relieving immunosuppression in the TME and activating T cells are the two key facets of their mechanism of action.

3.1.1. Activating T cells

CTLA-4 antibodies can sustain an activated state during the T cell activation stage, improving the capacity to assault tumor cells, by blocking the signals that prevent T cell activation. By interacting with CD28's B7-1 and B7-2 ligands, CTLA-4 lowers the second signal necessary for full T cell activation. By preventing CTLA-4 from attaching to its ligands, its antibodies allow T cells to get enough activation signals.

3.1.2. Relieving TME immunosuppression

CTLA-4 antibodies can block the immunosuppressive function of regulatory Treg cells. Treg cells in the TME express immunological checkpoint molecules including CTLA-4, which limit the action of effector Te cells, hence dampening the immune response. It can target Treg cells in the TME, inhibit the CTLA-4 pathway, and lower Treg cells' immunosuppressive function, allowing effector T cells to exert more anti-tumor activities. According to studies, the objective response rate (ORR) of the combination CTLA-4 antibody Ipilimumab and Nivolumab treatment for HCC is 32%, with a median survival time (MST) of 23 months. This indicates that this antibodies have a significant effect in relieving TME immunosuppression [15].

3.1.3. Clinical application, therapeutic efficacy and adverse reactions of CTLA-4 inhibitors in the treatment of HCC

CTLA-4 antibodies possess a powerful and long-lasting ability to activate the immune system, yet are prone to inducing immune-related adverse reactions. The most common ones include colitis, hepatitis, dermatitis, neuropathy, and endocrine disorders. In one study, the overall population showed good tolerance to the combined dual-immunotherapy, with 37% of patients having treatment-related adverse reactions of grade 3-4, and 5% of patients discontinuing treatment due to grade 3-4 adverse reactions [16]. Before each administration, it is necessary to carefully evaluate the relevant symptoms, signs, and clinical biochemical parameters of patients undergoing CTLA-4 immunotherapy. Only when it is confirmed that no severe adverse reactions of grade 3 or above have occurred can the drug be administered clinically.

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Currently, it has two targeted antibodies, Ipilimumab and Tremelimumab, which are utilized in the clinical treatment with melanoma, kidney cancer, prostate cancer, and lung cancer, which gives some precedent for their use in the treatment of HCC. Using the CheckMate 040 study as an example, the ORR was 32% for progressed HCC patients who had received sorafenib treatment and were then treated with the combined CTLA-4 antibody Ipilimumab and Nivolumab, with an MST of 23 months. This suggests that CTLA-4 inhibitors have some potential in the treatment of HCC.

3.2. The Mechanism of Action of PD-1/PD-L1 Inhibitors

3.2.1. Improving immune cells' recognition of tumor cells

PD-1/PD-L1 inhibitors are crucial in HCC immunotherapy because they prevent PD-1 binding to PD-L1, reduce the immune-suppressive signal, and activate T cells.

PD-1 is primarily expressed on the surface of activated T cells, whereas PD-L1 is strongly expressed on the surface of tumor cells. The two bind together and limit T cell activation, preventing immune cells from effectively detecting tumor cells. PD-1/PD-L1 antibodies can inhibit this interaction, allowing immune cells to better detect HCC cells. According to research, when using PD-1/PD-L1 antibodies to treat HCC, the tumor response rate (RR) is 14% - 23%, and the disease control rate (DCR) is 54% - 55%. This demonstrates that PD-1/PD-L1 antibodies can help immune cells recognize and kill tumor cells [17].

3.2.2. Maintaining T cell activity

PD-1/PD-L1 antibodies restore the inhibitory impact on T cells by preventing PD-1 from binding to PD-L1, which aids T cells in preserving their anti-tumor activity. The purpose of them is to impede the transcription and translation of genes and cytokines necessary for T cell activation, which is inhibited when PD-1 binds to PD-L1. This allows T cells to continue their anti-tumor actions.

3.2.3. Clinical application, therapeutic efficacy and differences of PD-1/PD-L1 inhibitors in the treatment of HCC

Regarding clinical use, PD-1/PD-L1 immunotherapy is a novel form of anti-cancer immunotherapy that is now receiving a lot of interest and may be able to treat a variety of tumor types. The FDA currently approves it for the treatment of kidney cancer, non-small cell lung cancer, and advanced melanoma. According to research findings, individuals with PD-L1 expression $\geqslant$ 1% can benefit from a 19% decrease in mortality risk from treatment. Patients with high PD-L1 expression (TPS $\geqslant$ 50%) experience more substantial survival benefits, with a 31% decrease in mortality risk, when compared to the population with low PD-L1 expression (1% $\leqslant$ TPS $\leqslant$ 49%) [18].

Currently, PD-1 antibodies that have been marketed in China include Nivolumab (O drug) and Pembrolizumab (K drug), and domestic it include Camrelizumab, Toripalimab, and Sintilimab. In the results of the international multicenter phase II single-arm clinical study Check-Mate 040, the tumor RR of using Nivolumab to treat advanced HCC was 14% - 23%.

4. Combined treatment of CTLA-4 and PD-1/PD-L1 inhibitors for HCC

4.1. Advantages of dual-immune combined treatment

4.1.1. Synergistic effect

In the fight against tumors, the dual-immune combination has a synergistic effect. CTLA-4 monoclonal antibodies relieve the signals that inhibit T cell activation, maintain the activated state of

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T cells, and simultaneously block the immunosuppression of Treg cells in the TME, mobilizing more "capable individuals" to participate the anti-tumor activities. By preventing PD-L1 on tumor cells from binding to B7-1 on the surface of T cells, PD-L1 monoclonal antibodies help T cells maintain long-term anti-tumor activity without affecting PD-L1 to PD-L2 binding, preserving the body's immune self-stability to lower the incidence of immune-related adverse reactions. Combined, they play a synergistic role of "ignition and startup," promoting continuous and rapid activation, massive proliferation, and transportation of Te cells, as well as jointly relieving the immune "brake" effect of tumor cells, allowing highly activated T cells to kill tumor cells quickly, significantly impairing tumor immune escape, and encouraging the immune system to kill tumor cells.

4.1.1.1. T cell activation stage

The dual-immune combination promotes the activation and proliferation of Te cells during the T cell activation stage by acting in concert. By attaching itself to B7 family molecules, CTLA-4 primarily prevents T cell activation and proliferation in the early stages of T cell activation. The use of CTLA-4 inhibitors can counteract this inhibitory action, boosting the activation of T cells. By preventing PD-1 from attaching to PD-L1 later in the T cell activation process, PD-L1 monoclonal antibodies help to sustain T cell activity. At this crucial stage, the two inhibitors support T cell activation and proliferation from various angles, enhancing the immune response against the tumor. Some studies have revealed through single-cell transcriptome analysis of patient samples that the dual-immune combination therapy enhances the expansion of CD4+ and CD8+ T cells, especially the obvious activation of CD4+ T cells [19]. In some clinical studies, the level of T cell activation in patients who received the combined treatment of CTLA-4 inhibitors and PD-L1 inhibitors was significantly higher than that in patients who accepted only one type of inhibitor. Single-cell transcriptome analysis of patient samples has shown that dual-immune combination therapy enhances the expansion of those two cells, particularly the evident activation of CD4+ T cells [20].

The dual-immune combination is also crucial throughout the stage of T cell migration to tumor tissue. By lowering the quantity of immunosuppressive cells, including Tregs, that prevent Te cells from migrating to tumor tissue, CTLA-4 inhibitors can change the makeup of immune cells in the TME and improve the environment for Te cell migration. In the meantime, PD-L1 inhibitors can promote the directed migration of T cells to tumor tissue by increasing the expression of chemokine receptors on the surface of T cells. For example, in HCC patients who received the dual-immune combined treatment, immunohistochemical analysis showed that the infiltration of T cells in the tumor tissue was significantly increased, proving that the dual-immune combination therapy can encourage T cells to migrate to tumor tissue more efficiently.

4.1.1.2. T cell recognition of tumor cells and killing stage

The dual-immune combination strengthens the immune system's response to tumors during the period when T cells recognize and eliminate tumor cells. By preventing PD-1 from attaching to PD-L1, PD-L1 drugs increase T cell activation and improve their ability to identify tumor cells. In the meantime, CTLA-4 inhibitors can increase Te cells' capacity to destroy tumor cells by lowering the quantity of immunosuppressive cells in the TME. For instance, in several clinical trials, patients who received the dual-immune combination treatment had higher levels of activated cytotoxic T lymphocytes (CTLs) in their tumor tissue, and their tumor cells' rate of apoptosis also increased dramatically. This suggests that the dual-immune combination treatment enhances the anti-tumor immune response by playing a significant synergistic function in the stage of T cell detection of tumor cells and destruction.

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4.1.1.3. Fostering long-term immune memory formation

The dual-immune combination can also promote the formation of long-term immune memory. When those two inhibitors are used in combination, more T cells can be activated. These T cells will form long-term immune memory during the process of killing tumor cells. When the tumor reappears, these T cells with immune memory can be quickly activated to play an anti-tumor role [21]. The formation of this long-term immune memory helps to improve the long-term survival rate of patients and reduce the recurrence and metastasis of tumors.

4.1.1.4. TME regulation

The dual-immune combination also has a significant synergistic effect in the TME. By lowering the quantity of immunosuppressive cells like Tregs and myelogenous suppressor cells (MDSCs) and raising the quantity and activity of anti-tumor immune cells like CTLs, the combination therapy can control the makeup and activity of the immune cells present. Among these, CTLA-4 inhibitors can lessen Tregs' effectiveness and quantity, which will lessen their inhibitory influence on Te cells.

4.1.2. Analysis of efficacy differences based on viral etiology

HCC is a highly heterogeneous disease with significant differences among patients in terms of the TME, immune status, and viral infection status. The efficacy of combined treatment varies among different viral infection subgroups.

For example, research has found that compared with NSCLC patients who do not express PD-1L, those with positive PD-1L expression have longer PFS (HR = 0.46, P = 0.014) and the overall survival (OS)(HR = 0.26, P = 0.002). Patients with positive PD-L1 expression on tumors or immune cells in the TME may be more sensitive to the treatment with PD-1/PD-L1 inhibitors [22]. Additionally, for HCC patients with hepatitis B virus infection, the combined treatment effect is more significant, and antiviral treatment is closely related to the improvement of survival. For such patients, antiviral treatment can be strengthened while undergoing combined immunotherapy to improve the treatment effect. The global pharmaceutical company AstraZeneca announced the outcomes of the HIMALAYA phase 3 trial on September 16, 2024. The data showed that 19.6% of patients with advanced, unresectable HCC who were treated with the STRIDE regimen and had not received systemic treatment and were not suitable for local treatment were still alive five years after treatment, compared to a historical rate of roughly 7%. Patients had a 24% lower chance of dying when compared to those receiving Sorafenib as part of the usual therapy regimen. Five years after starting the STRIDE regimen, 28.7% of patients with successfully managed conditions were still alive, compared to 12.7% of patients in the Sorafenib treatment group. Comparatively speaking, although the prognosis of combined immunotherapy for advanced HCC patients is not ideal, it can effectively improve the survival period.

4.1.3. Safety of combined treatment

The HCC immunological microenvironment is quite intricate. Vascular endothelial growth factor (VEGF), Tregs, and other factors are involved in addition to ICs like CTLA-4 and PD-1/PD-L1. As a result, the immune microenvironment may not be completely regulated by the simple combination of these two inhibitors; other therapeutic approaches may be required.

There may be certain negative effects from the dual-immune combined treatment of liver cancer. One study, for instance, discovered that the probability of immune-related adverse events was as high as more than 50% when anti-CTLA-4 and anti-PD-1 antibodies were used together to treat melanoma, compared to roughly 30% and 20%, respectively, when they were used alone. In grades 3–4, the dual-

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immune combination treatment has an incidence of treatment-related negative outcomes of around 35.1%, according to statistics [23]. Furthermore, CTLA-4 is more likely than PD-1 and PD-L1 to produce liver damage; when these two factors are combined, the incidence of liver damage is much higher than it is with single-immune therapy.

Currently, there aren't enough reliable biomarkers to predict the effectiveness and side effects of combined treatment, so more biomarker research is needed to better screen patients who are a good fit for combined treatment, increasing treatment efficacy and pertinence. Clinical Data Analysis of the dual-immune combined treatment

4.2. Evidence from preclinical studies

The combined administration of these two inhibitors has demonstrated a synergistic anti-tumor effect in preclinical studies in a variety of tumor models, including a mouse tumor model, where the combined treatment may significantly reduce tumor growth and extend the survival period of mice [24]。The study treated the mice 3 or 10 days after inoculating them with mouse colon or mouse ovarian cancer cells respectively. It takes about 14 days to render the tumor-reactive T cells, which are initially functional in response to the cancer cell inoculation, dysfunctional. Using tumors that are at least 14 days old and exceed 100 mm^3, inoculating bacteria that produce antigens and combining with PD-1 blockade can eradicate the tumors [25].

4.3. Clinical research data

Currently, in the treatment of HCC, the efficacy rate of single-drug therapy is relatively low. For example, a study showed that the ORR of the PD-1 inhibitor nivolumab in the treatment of liver cancer is only about 20%.

Both of these inhibitors have achieved certain therapeutic effects. Regarding the efficacy of combined treatment, multiple clinical studies are currently being evaluated. For example, in the CheckMate 040 study, the ORR of the combined treatment of nivolumab and ipilimumab was 32%, and the DCR was 54%. In addition, a phase I/II study evaluated the effect of the combined treatment of durvalumab and tremelimumab on HCC, with an ORR of 25.0% and a DCR of 57.5%. These data indicate that the combined treatment shows better efficacy than single-drug treatment in the treatment of liver cancer.

The data results of the latest research on the STRIDE regimen of dual-immune combination in unresectable HCC - the HIMALAYA phase 3 trial announced by the global pharmaceutical company AstraZeneca: It includes 1171 patients who received the dual-immune treatment regimen STRIDE composed of Durvalumab and Tremelimumab. The STRIDE group has 393 patients, whereas the durvalumab and sorafenib groups each contain 389 patients. Comparing the OS benefits of the STRIDE and sorafenib groups is the aim of this study. The findings revealed that the STRIDE group had a median overall survival (mOS) of 16.43 months, followed by the durvalumab group at 16.56 months and the sorafenib group at 13.77 months. The three groups' respective 3-year OS rates were 30.7%, 24.7%, and 20.2%. The OS hazard ratio of the STRIDE group to the sorafenib group was 0.78 (96.02% confidence interval: 0.65 - 0.93; P = 0.0035). It can be seen that the patients in the STRIDE group have a significant benefit in terms of OS. This has for the first time confirmed that the dual-immune combination regimen can achieve OS improvement compared with the standard treatment of sorafenib, and this result provides strong support for the immunological combined treatment of HCC.

5. Conclusion

This study has thoroughly explored the regulatory mechanisms of ICs pathways in the TME and the impacts of immunotherapy for HCC under the combined treatment of these two inhibitors:

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The PD-1/PD-L1 pathway allows tumor cells to evade immune system attacks by preventing T cell activation, proliferation, and cytokine release; the CTLA-4 pathway prevents T cell activation by interacting with CD28 ligands to decrease the second signal necessary for full T cell activation; inhibitors of of the former improve the survival of HCC patients by improving immune cell recognition of tumor cells and sustaining T cell activity; as ICs inhibitors, inhibitors of the latter enhance the ORR of liver cancer treatment and the MST of patients by activating T cells and relieving immunosuppression in the TME.

Currently, whether the use of inhibitors alone or in combination can improve HCC is being explored based on the existing research data and multiple ongoing prospective studies. In general, the clinical research data of patients collected on the basis of the existing evidence indicate that ICs inhibitors, especially in combination with combined treatment, are expected to become a good approach for the effective treatment of liver cancer.

Currently, there are still many deficiencies in the understanding of this paper. In the future, the specific role and mechanism of ICs molecules in the occurrence and development of HCC can be further explored in depth, with efforts dedicated to reducing adverse reactions and optimizing combined treatment to improve the therapeutic effect. By conducting in-depth research on ICs pathway mechanisms, optimizing combined treatment regimens, and developing personalized treatment strategies, etc., it is expected to provide more effective immunotherapy methods for liver cancer patients and improve their prognoses through these efforts.

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