Recent Advances in Cancer Treatment with PD-1/PD-L1 Inhibitors

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Abstract: This study reviews recent advances in the clinical use of PD-1/PD-L1 blocking agents for cancer therapy with a specific focus on their utilization in non-small cell lung carcinoma, colorectal carcinoma, hepatocellular carcinoma, and endometrial carcinoma. Traditional cancer therapies have inherent limitations, whereas these inhibitors exert antitumor effects through impeding the interplay between them, thereby restoring T-cell activity, with distinct mechanisms observed across different cancer types. The objective of this research is to optimize treatment regimens, analyze factors affecting therapeutic efficacy, explore the mechanisms of action, and identify optimal combination therapies, aiming to offer a reference for clinical practice

Keywords: PD-1/PD-L1; Immunotherapy

1. Introduction

Cancer, also known as malignant tumors, constitutes a category of illnesses arising from unregulated abnormal cell growth. Cancer cells evade genetic regulation, exhibit unrestricted proliferation, and metastasise to other parts of the body via the bloodstream and lymphatic system, forming new tumors. Malignancy has emerged to rank among the primary contributors to mortality worldwide, encompassing a multitude of subtypes such as pulmonary carcinoma, mammary carcinoma, colorectal carcinoma, and hepatic carcinoma. In the long-term practice of cancer treatment, surgery, radiotherapy, and chemotherapy remain the most widely applied conventional therapies, yet each exhibits significant limitations. Surgery often can't completely eradicate all cancer cells and involves substantial surgical trauma, potentially impairing the patient's physical functions. Radiotherapy, while destroying cancer cells, also damages normal tissues surrounding the tumor, leading to a range of side effects and limited therapeutic efficacy. Cancer cells readily develop resistance to chemotherapy drugs, diminishing treatment efficacy over time and potentially leading to failure.

Immunotherapy has represented a major breakthrough in cancer treatment in recent years, operating through a fundamentally different mechanism from traditional therapies. It offers high specificity, minimal side effects, and sustained efficacy, preventing recurrence while demonstrating significant potential for combination therapies.

2. Literature Review

2.1 Principles and Mechanism of Action of PD-1/PD-L1 Inhibitors

PD-1, also designated as CD279, belongs to the immunoglobulin superfamily, analogous to CD28. This molecule is mapped to chromosome 2q37.3 and is predominantly found on the surface of activated T cells, B cells, and myeloid cells. Its cognate ligands include PD-1 and PD-L1[1], further activate or inhibit the downstream PI3K/AKT/mTOR signaling pathway [2] Besides, PD-1 can also send negative regulatory signals. Within cell signaling networks, the MAPK/ERK cascade functions as a core transducer of mitogen signals.

Both pathways constrain T-cell proliferation and downregulate cytokine secretion (including IL-2, IL-10, and IFN-γ) [3], which in turn promotes T-cell dysfunction or triggers T-cell apoptosis.

PD-1/PD-L1 blockers achieve their therapeutic action by disrupting the interaction between them, thereby relieving the inhibition of TCR and CD3 co-stimulatory signals in T cells. This enables the normal activation of downstream PI3K/AKT and MAPK signaling pathways, facilitating the restoration of T cell proliferation and secretory functions [4]. Consequently, in the management of malignancies such as mCRC, their inhibitors also counteract tumor immune evasion through T cell motivation, thereby reestablishing immune function. Furthermore, their mechanisms of action differ across various

cancer types.

2.2.1 Non-small cell lung cancer

Mechanistic characteristics:

In certain patients with NSCLC, particularly those with lung adenocarcinoma, tumor cells exhibit positive PD-L1 expression, accompanied by a measurable degree of T-cell infiltration within the tumor microenvironment associated with clinical prognosis. Through blockade of this signaling pathway, PD-1/PD-L1 inhibitors are capable of remodeling the patient's immune landscape and potentiating anti-tumor immune responses [5]. Additionally, chemotherapeutic agents such as cisplatin and carboplatin can reset the immune microenvironment, converting cancer cells into "hot tumors" characterized by abundant infiltration of effector T cells and high PD-L1 expression-an effect that augments the efficacy of PD-1 inhibitors. Pemetrexed and taxanes, on the other hand, can elevate the levels of $CD4^+$ and $CD8^+$ T cells while selectively reducing the counts of regulatory T cells (Treg) and myeloid-derived suppressor cells.

Clinical research data:

Serplulimab in combination with chemotherapy confers survival benefits to patients, marking the first confirmation of the efficacy of PD-1 inhibitors in extensive-stage small cell lung cancer (ES-SCLC). The RATIONALE 312 median overall survival (OS) among patients assigned to the PD-1 inhibitor tislelizumab plus chemotherapy arm in a clinical trial was 15.5 months, which supported the clinical application of this therapeutic strategy. [6]. Additionally, a phase II clinical trial (NCT04790539) indicated that camrelizumab in combination with chemotherapy exhibits favorable efficacy and controllable safety as first-line therapy for ES-SCLC [7]. The median overall survival (OS) of 15.5 months, observed in patients assigned to the PD-1 inhibitor tislelizumab plus chemotherapy arm of a phase Ⅲ multicenter clinical trial, holds significant clinical implications: not only does it support the application of this therapeutic strategy in routine clinical practice, but it also provides a reference for optimizing treatment sequences in patients with advanced cancers-especially those with high PD-L1 expression, who may derive greater benefit from the immunotherapy-chemotherapy combination.

Current challenges/considerations:

In the clinical practice of immunotherapy for non-small cell lung cancer (NSCLC), the treatment response rate remains significantly influenced by two key biological factors: first, the patient's PD-L1 expression status-where high PD-L1 expression (e.g., TPS ≥ 50%) enhances the binding of immune checkpoint inhibitors to PD-1/PD-L1, thereby strengthening anti-tumor T-cell activation and improving response rates; second, the tumor mutation load (TMB)-higher TMB leads to more tumor-specific neoantigens, which are more likely to be recognized by the immune system, thus increasing the probability of effective immunotherapy response. It is necessary to further explore biomarkers to accurately select the population that can benefit from it. At the same time, the optimization of combined treatment regimens, such as the selection of chemotherapeutic drugs and the timing of administration, still needs more clinical data support.

2.2 Colorectal Cancer (CRC)

Mechanistic characteristics:

PD-1/PD-L1 blockers avoid the interaction between them, which removes the blockage of TCR and CD3 co-stimulatory signal transmission on T cells, enabling the normal activation of downstream PI3K/AKT and MAPK pathways and restoring the proliferation and cytokine secretion activities of T cells [8]. It is inferred that in the course of treating metastatic colorectal cancer (mCRC), this type of inhibitor can restore the body's immune function by activating T cells, thereby playing a role in resisting tumor immune escape.

Clinical research data:

Currently, common PD-1/PD-L1 inhibitors employed in clinical trials for mCRC encompass nivolumab, pembrolizumab, and durvalumab. These drugs have achieved significant efficacy in 4%-5% among mCRC cases with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR). However, these agents exhibit suboptimal effectiveness in over 90% of microsatellite stable (MSS)/mismatch repair-proficient (pMMR) mCRC cases [9].

Current challenges/considerations:

MSS/pMMR mCRC has a low response rate to single-agent PD-1/PD-L1 inhibitors, so it is necessary to explore combined strategies, like combining immunotherapy with chemotherapy or anti-angiogenic drugs, to improve efficacy. At the same time, it is necessary to identify the beneficial biomarkers and optimal combination

regimens for patients with this subtype.

2.3 Hepatocellular Carcinoma

Mechanistic characteristics:

These inhibitors are often used with CTLA-4 inhibitors. CTLA-4 is an inhibitory proteinaceous receptor predominantly expressed on activated $CD4^+$, $CD8^+$ T cells, and Treg cells [10]. It connects to B7 molecules, leading to T-cell unresponsiveness and participating in the negative regulation of the immune response. Studies have shown that the overexpression of CTLA-4 where the Upregulation of a target substance in tumor cells raises its concentration in the tumor microenvironment, which in turn impairs T-cell activation and diminishes the immune system's anti-tumor response[11].

Clinical research data:

After phase I and II trials, nivolumab combined with ipilimumab received FDA approval as a second-line treatment for hepatocellular carcinoma following the failure of sorafenib therapy [12]. In addition, the combined use of camrelizumab, apatinib, and hepatic artery infusion chemotherapy has shown effectiveness and safety [13]. A study by Huang Jingzheng et al. [14] in a clinical study involving 94 patients diagnosed with advanced hepatocellular carcinoma (HCC), results showed that compared with the regimen of transcatheter arterial chemoembolization (TACE) combined with lenvatinibTACE + lenvatinib + PD-1 monoclonal antibody could enhance treatment response and extend progression-free survival (PFS) as well as overall survival (OS).

Current challenges/considerations:

Although combined therapy improves efficacy, it may increase the incidence of adverse reactions, so it is essential to balance efficacy and safety. For patients with large liver cancer or advanced disease complicated by portal vein tumor thrombus and distant metastases, simple interventional therapy is difficult to completely block the blood supply, and the individualized selection of combined regimens still needs to be optimized.

2.4 Endometrial cancer

Mechanistic characteristics:

PD-1 immune checkpoint inhibitors can restore T-cell vitality and trigger autoimmune responses. PD-L1 inhibitors have strong targeting to PD-L1 expressed by tumor cells and are less likely to cause T lymphocytes to damage normal tissues [15]. In addition, patients who are resistant to PD-1 inhibitors may still respond to PD-L1 inhibitors.

Clinical research data:

Pembrolizumab has received FDA clearance for treating MSI-H or dMMR solid tumors, including endometrial cancer. Supporting this authorization, a phase II clinical trial by Le et al. investigated the efficacy and safety of Pembrolizumab in patients with advanced MSI-H/dMMR solid tumors, with a subset of participants having endometrial cancer[16-17] showed that the objective response rate (ORR) of pembrolizumab in the treatment of dMMR tumors reached 53.3%, the disease control rate (DCR) reached 73.3%, and 78% of patients with MSI-H tumors had a response lasting at least 6 months. The multi-cohort phase Ib KEYNOTE-28 study confirmed that pembrolizumab has good and long-lasting anti-tumor efficacy in previously treated advanced PD-L1-positive endometrial cancer patients [18]. The multi-cohort phase II KEYNOTE-158 study indicated that it can be used for unresectable or metastatic MSI-H/dMMR endometrial cancer patients who have progressed after previous treatment and have no alternative treatment options [19].

Current challenges/considerations:

For non-MSI-H/dMMR endometrial cancer patients, single-agent immunotherapy has limited efficacy, so it is necessary to explore combined treatment ways. At the same time, it is necessary to clarify the mechanism of immune resistance and reversal methods to expand the population that can benefit from treatment.

3. Conclusions

3.1 Non-small Cell Carcinoma

PD-1/PD-L1 blockers in combination with chemotherapy showed no significant rise in the rate of adverse reactions when contrasted with chemotherapy alone, with bone marrow suppression remaining the primary adverse effect [20]. Close monitoring of patients' blood counts is required during treatment. However, the following limitations remain: PD-L1 expression was not assessed; the small number of included cases and limited sample size precluded stratified analysis; more comprehensive, robust, and detailed findings require substantial clinical research data to support.

3.2 Rectal Cancer

PD-1/PD-L1 inhibitors are currently a focus of clinical research in mCRC, yet their mechanisms in mCRC treatment remain incompletely understood.

Fully understood. While PD-1/PD-L1 inhibitors have gained clinical recommendation for treating MSI-H/dMMR mCRC, they are subject to constraints such as high treatment costs. For MSS/pMMR mCRC, PD-1/PD-L1 inhibitor immunotherapy remains in the clinical trial phase, with most trial results indicating limited benefit for MSS/pMMR mCRC patients.

Remain in the clinical trial phase. Most trial results indicate that the benefit for MSS/pMMR mCRC patients is not entirely satisfactory

Consequently, exploring suitable treatment strategies for MSS/pMMR mCRC patients remains a current research priority.

3.3 Hepatocellular Carcinoma

Multiple phase III trials for HCC are currently underway, alongside clinical studies investigating PD-1/PD-L1 inhibitors in combination with molecularly targeted agents and local treatments such as interventional procedures. However, while immunotherapy combined with other regimens enhances efficacy, it also markedly increases adverse reactions in patients. Therefore, for HCC patients with different indications, selecting the optimal regimen, appropriate dosage, and timing under the premise of improving efficacy, enhancing prognosis, and ensuring safety is key to future immunotherapy combination treatments for liver cancer.

3.4 Endometrial Cancer

The mechanisms of immune checkpoint inhibitor therapy are highly complex. Further exploration of combining CTLA-4 and PD-1/PD-L1 immune checkpoint inhibitors with immunotherapy, targeted therapy, oncolytic viruses, and tumor vaccines holds promise for further efficacy enhancement.

Regarding the application of PD-1/PD-L1 inhibitors across various cancers, numerous critical avenues remain to be explored. For non-small cell lung cancer, expanding sample sizes and conducting stratified analyzes incorporating PD-L1 expression testing are essential to inform treatment optimization.

In rectal cancer, efforts should focus on overcoming treatment bottlenecks for MSS/pMMR patients while exploring ways to reduce treatment costs for MSI-H/dMMR patients, thereby making effective therapies more accessible.

For hepatocellular carcinoma, in-depth investigation of immunotherapy combination regimens is required. This should enhance efficacy while rigorously managing adverse reactions, enabling precise selection of optimal regimens, dosages, and timing for patients with different indications.

Regarding endometrial carcinoma, further clarification of the therapeutic mechanisms of immune checkpoint inhibitors is required, alongside active exploration of their combination with other therapies to enhance treatment outcomes. Through these ongoing investigations, PD-1/PD-L1 inhibitors may achieve greater value in cancer treatment.

4. Development and Outlook

As a pivotal breakthrough in cancer immunotherapy, PD-1/PD-L1 inhibitors have exhibited substantial potential in the treatment of multiple malignancies, encompassing non-small cell lung cancer, colorectal cancer, hepatocellular carcinoma, and endometrial carcinoma. Nevertheless, their clinical application remains confronted with numerous challenges. Future research ought to concentrate on in-depth exploration in the following areas to promote efficacy enhancement and clinical translation.

4.1 Non-Small Cell Lung Cancer

Precision Stratification and Regimen Optimization. Existing studies confirm that their blockers combined with chemotherapy prolong patient survival with manageable safety profiles. However, limitations such as small sample sizes and the absence of PD-L1 expression-based stratification restrict the generalisability of these findings. Future research should expand clinical sample sizes while strengthening monitoring of long-term adverse reactions (e.g., immune-related toxicity) to provide more precise grounds for personalized treatment.

4.2 Colorectal Cancer

Overcoming Subtype Limitations and Reducing Treatment Costs. For metastatic colorectal cancer (mCRC) of the MSS/pMMR subtype, which accounts for over 90% of cases,

PD-1/PD-L1 inhibitors demonstrate limited efficacy as monotherapy. Priority should be given to exploring combination strategies, such as co-administration with chemotherapy, targeted therapies (e.g., VEGF inhibitors), or local treatments (e.g., radiotherapy) to enhance efficacy by remodeling the tumor microenvironment (e.g., increasing T-cell infiltration). Concurrently, for patients with proven efficacy in MSI-H/dMMR tumors, reducing treatment costs through drug innovation and optimizing healthcare policies is essential to improve treatment accessibility. Of particular note, the combination of VEGF inhibitors and PD-1/PD-L1 inhibitors stands out as a key therapeutic pairing: VEGF inhibitors help improve the tumor microenvironment (e.g., by normalizing abnormal blood vessels and decreasing the number of immunosuppressive cells), while PD-1/PD-L1 inhibitors stimulate the activation of T cells. Together, these two types of drugs create a synergistic effect that boosts treatment efficacy. From a clinical perspective, available options include the three-drug regimen of "VEGF inhibitor + PD-1/PD-L1 inhibitor + chemotherapy" (designed to achieve stronger therapeutic effects) and the chemo-free dual-target combination (which is safer for patients who cannot tolerate chemotherapy).

At the same time, for mCRC patients with the MSI-H/dMMR subtype-who have been shown to respond effectively to PD-1/PD-L1 inhibitors-reducing treatment expenses through innovations in drug development and the optimization of healthcare policies is vital. This effort is essential to increase the accessibility of effective treatments for these patients.

4.3 Hepatocellular Carcinoma

Combination regimens conclude efficacy. Combination regimens of PD-1/PD-L1 inhibitors with CTLA-4 inhibitors, molecularly targeted drugs, or interventional therapies (e.g., TACE) have demonstrated synergistic antitumour effects, albeit with increased adverse reaction rates. Future clinical trials should identify optimal combination regimens tailored to disease stage (e.g., intermediate vs. advanced) and comorbidities, achieving an optimal "efficacy-safety" balance.

4.4 Endometrial Carcinoma

Mechanistic Elucidation and Expansion of Combination Therapies. The efficacy of PD-1/PD-L1 inhibitors PD-L1-positive patients has been validated, though their precise mechanisms (such as cross-regulation with other immune checkpoints) require further clarification. Future research should explore combination therapies with CTLA-4 inhibitors, oncolytic viruses, and tumor vaccines to synergistically enhance immune responses through multi-targeted approaches. Concurrently, identifying novel biomarkers (such as immune microenvironment characteristics) will further refine treatment precision.

PD-1/PD-L1 blockers have pioneered novel pathways in cancer treatment, yet their full clinical value hinges upon a deepened understanding of the biological characteristics of different cancer types, personalized optimization of treatment regimens, and sustained advancement in translational medicine.

5. Challenge and Future

5.1 Common Challenges

Although the application of their blockers in various cancers has achieved breakthroughs, there are still common cross-cancer challenges:

5.1.1 Management of immune-related adverse events (irAEs)

Patients with different cancers may experience irAEs such as rash, colitis, and pneumonia after receiving immunotherapy, and some severe reactions can be life-threatening. At present, the mechanism of irAEs is not fully clarified, and there is no unified standard for graded diagnosis and treatment. Clinically, it is necessary to balance the therapeutic benefits and safety, especially for patients with underlying diseases, individualized monitoring is required.

5.1.2 Standardization and accessibility of biomarker detection

Biomarkers including PD-L1 expression level, tumor mutational burden (TMB), and microsatellite instability (MSI) serve as a key foundation for forecasting therapeutic efficacy. However, there are differences in detection methods (such as antibody clone numbers and scoring standards) among different institutions, which may lead to inconsistent results. At the same time, the detection technology in some primary medical institutions is limited, which restricts the popularization of accurately screening beneficiary populations.

5.1.3 Complexity of drug resistance mechanisms

Primary resistance (no response at the initial stage of treatment) and secondary resistance (recurrence after treatment) are common in various cancers. The mechanisms involve tumor microenvironment remodeling (such as infiltration of immunosuppressive cells), abnormal activation of signaling pathways (such as PI3K/AKT mutation), and loss of neoantigens, and no effective reversal strategies have been formed yet.

5.2 Future Prospects: Exploration of Novel Immune Combination Therapies

In addition to optimizing existing combination regimens, future efforts should focus on exploring innovative immune combination strategies to break through current treatment bottlenecks:

5.2.1 Bispecific antibodies

Bispecific antibodies that target both and other immune checkpoints (such as CTLA-4, LAG-3) can synergistically relieve immune suppression, enhance T-cell activation, and reduce the risk of monotherapy resistance. For example, bispecific antibodies targeting PD-1/CTLA-4 have shown a better efficacy-safety balance in solid tumors.

5.2.2 Combination of antibody-drug conjugates (ADCs) and immunotherapy

ADC drugs can directly kill tumor cells by targeted delivery of cytotoxic drugs, and release tumor-associated antigens (TAAs) to enhance immunogenicity, which can synergistically activate systemic anti-tumor immune responses with PD-1/PD-L1 inhibitors. At present, clinical trials of ADC combined with immunotherapy in breast cancer, gastric cancer and other fields have shown initial results.

5.2.3 Synergy between personalized tumor vaccines and immune checkpoint inhibitors

Personalized vaccines designed based on patients' tumor mutation profiles can induce specific T-cell responses. Combined with PD-1/PD-L1 inhibitors, they can further expand the range of immune responses, which may have breakthrough value especially for low-immunogenic tumors (such as MSS colorectal cancer).

These novel combination strategies are expected to provide new directions for overcoming drug resistance and improving broad-spectrum efficacy by regulating the immune system in multiple dimensions, but their safety and long-term benefits still need to be verified by large-scale clinical trials.

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