Combined Strategy of Targeted Therapy and Immunotherapy for Bladder Cancer

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Abstract. Bladder cancer is a highly prevalent malignant tumor in the urinary system worldwide, and the treatment has been long facing significant challenges. Immunotherapy represented by PD-1 (programmed death receptor-1)/PD-L1 (programmed death ligand-1) inhibitors and targeted therapies such as antibody-drug conjugates have already changed the landscape. However, the efficacy of a single drug is limited, and the problem of drug resistance is quite prominent. The combined treatment strategy, through the deep synergy of pharmacology and immunology, aims to overcome tumor heterogeneity and immunosuppressive microenvironments. It has become a core research direction in the treatment of bladder cancer. This review systematically elaborates the synergistic biological mechanisms by which targeted drugs induce immunogenic cell death, re-adjust the tumor immune microenvironment, and immune checkpoint inhibitors amplify and prolong the therapeutic effect. It focuses on elaborating the groundbreaking clinical evidence achieved by the "ADC + immunotherapy" approach, such as ennozumab combined with pembrolizumab, in advanced first-line and neoadjuvant treatments, and also summarizes the emerging methods including dual immunotherapy combinations, immunotherapy combined with other regulators, and oncolytic viruses. Furthermore, this article thoroughly examines the challenges that may arise from combined treatment, such as the complexity of drug resistance mechanisms and the optimization of drug toxicity management. Finally, a series of prospects were presented regarding future directions such as the development of drugs targeting new targets in the tumor microenvironment. This article aims to provide an academic reference for a comprehensive understanding of the current status and future prospects of targeted and immunotherapy combined strategies for bladder cancer.

Keywords: bladder cancer, targeted therapy, immunotherapy, combined therapy.

1. Introduction

Bladder cancer is a common type of cancer worldwide. The number of cases has been increasing over the years, and both its incidence rate and mortality rate pose a significant burden on public health [1]. Based on the severity of its onset, bladder cancer is mainly classified into non-muscular-invasive bladder cancer (NMIBC) and muscular-invasive bladder cancer. The latter is more prone to metastasis and has a poorer prognosis [2]. The traditional standard treatment for advanced bladder cancer or metastatic urothelial carcinoma mainly involves chemotherapy based on cisplatin. However, the objective response rate is approximately 50-70%, and it often comes with significant side effects such as nephrotoxicity, neurotoxicity, and myelosuppression, which makes many patients unable to tolerate it due to their physical conditions [2, 3]. Although bladder perfusion immunotherapy using Bacillus Calmette-Guérin (BCG) is effective for some (NMIBC) superficial bladder cancers, there are issues such as lack of response, recurrence, and local side effects [4].

In recent years, the two revolutionary advancements in the field of tumor treatment - immune checkpoint inhibitors and molecular targeted therapy - have brought new hope to bladder cancer patients. For inhibitors targeting programmed death receptor-1 and its ligands, etc., they can eliminate the inhibition of tumors on T cells, thereby restoring the body's anti-tumor immune response. PD-1 (Programmed Death Receptor-1) not only helps the patient's body to become tolerant but also regulates the response of their own cells. This can prevent autoimmune diseases, but it can also prevent the immune system from killing cancer cells. PD-L1 is the ligand of PD-1, and it is expressed on antigen-presenting cells, some epithelial cells, and placental trophoblast cells, exerting immunoregulatory functions [5]. Meanwhile, drugs targeting specific molecular targets, such as those

targeting fibroblast growth factor receptors, have achieved precise strikes against bladder cancer cells [3].

However, the limitations of single-drug treatment are becoming increasingly evident. Immune checkpoint inhibitors are only effective in a subset of patients, and the overall response rate still needs to be improved. Their efficacy is limited by the suppressed state of the tumor immune microenvironment [1,3], and thus they cannot fully realize their potential benefits. However, targeted therapy is confronted with the challenges of tumor heterogeneity and secondary resistance. Therefore, by combining these two strategies and leveraging the complementary advantages of both to create a synergistic effect, it is possible to break through the limitations of single therapy, expand the group of beneficiaries, and delay or overcome drug resistance. The combination of immunotherapy and targeted therapy has become an inevitable trend and a cutting-edge hotspot in contemporary clinical and basic research [3]. This review will systematically explore the biological basis, key clinical evidence, current challenges and future development directions of this combined strategy for bladder cancer targeted immunotherapy.

2. Combined Treatment Strategy

The theoretical basis of combined therapy lies in the multi-dimensional and dynamic interaction between targeted drugs and immunotherapy, and its synergistic effect is far greater than the simple addition of individual therapies. Targeted immunotherapy combined with treatment not only acts on tumor cells themselves, but also improves the immune microenvironment of bladder cancer, induces immunogenic cell death, thereby enhancing the therapeutic effect of bladder cancer and improving the quality of life of patients.

2.1. Targeted Therapy

The traditional medical perspective holds that targeted drugs only act on tumor cells themselves. Modern research has revealed that they have a profound impact on the tumor immune microenvironment, creating excellent conditions for immunotherapy. Targeted therapy can enhance the efficacy against bladder cancer by reversing the immunosuppressive microenvironment and inducing the death of immunogenic cells.

2.1.1. Reversal of Immunosuppressive Microenvironment

Tumors create an inhibitory immune microenvironment by regulating regulatory T cells, recruiting myeloid-derived suppressor cells, and M2-type tumor-associated macrophages, which is a key factor leading to the failure of immunotherapy [1]. The research has found that there is a subgroup of macrophages with high expression of TREM2 in bladder cancer. TAM can undergo polarization under different tissue environments and the action of cytokines and differentiate into the classical activation type (M1) and the alternative activation type (M2). M1 exerts anti-tumor effects by secreting pro-inflammatory factors such as IL-12 and TNF-α, while M2 promotes tumor progression through anti-inflammatory factors like IL-10 and TGF-β. The metabolic reprogramming of M2 is closely related to its immunosuppressive function [1, 6]. Targeted therapy profoundly reshapes the immunosuppressive microenvironment of bladder cancer by regulating key oncogenic signaling pathways. Among them, the abnormal activation of the PI3K/AKT pathway (often driven by PTEN loss or PIK3CA gene mutation) mainly enhances the anti-apoptotic ability and metabolic activity of tumor cells, promoting their survival. Some targeted drugs can down-regulate key immunosuppressive factors such as VEGF and transforming growth factor-β (TGF-β) by inhibiting the PI3K/AKT and MAPK pathways. This can improve the tumor microenvironment in multiple ways: 1. Alleviate immune suppression: The reduction of VEGF can inhibit the abnormal vascular nutrient supply it provides for tumor growth, while the reduction of TGF-β can weaken its inhibition of the function of effector T cells and reduce its ability to induce epithelial-mesenchymal transition. 2. Enhancing the physical barrier: The secretion of factors such as TGF-β decreases, which can reduce the activity of cancer-associated fibroblasts and the abnormal remodeling of the extracellular matrix.

This, in turn, reduces the physical barriers that hinder the infiltration of immune cells and promotes the infiltration of cytotoxic T lymphocytes. Promoting the infiltration of cytotoxic T lymphocytes (CTLs, mainly CD8+ T cells) can have a direct anti-tumor effect on bladder cancer. The increased infiltration of CTL cells can directly recognize and kill tumor cells. Empirical experiments have shown that when the G3BP1-PI3K/AKT axis is inhibited using drugs to increase the expression of MHC-I in tumor cells, the infiltration of CD8+ T cells into the tumor in the mouse bladder cancer model significantly increases, and the killing ability against tumor cells also enhances, resulting in a reduction in tumor volume and weight [7,8]. This demonstrates that by targeting the tumor environment within the patient's body and promoting the entry of more immune cells capable of killing cancer cells into the tumor, this is a key mechanism for enhancing the body's immune response and delaying the deterioration of bladder cancer.

2.1.2. Induction of Immune-Dependent Cell Death

Inducing immune-mediated cell death is a specific type of cell death. While the tumor cells are eliminated, it also releases "danger signals" such as tumor-associated antigens and calreticulin. These signals can be regarded as providing the immune system with an extremely precise "identification map of friend and foe" [2]. This not only kills the tumor cells in the patient's body but also does not harm the normal immune cells and other cells. That is to say, it kills the cancer cells of bladder cancer without harming other cells, thereby improving the therapeutic effect and the quality of life of the patients.

Immunogenic cell death is a specific form of stress-induced cell death. ICD is different from the ordinary, silent cell apoptosis. Instead, it can activate the body to generate an adaptive immune response against tumors and may even form long-term immune memory [9]. The release of toxic payloads by ADC drugs within tumor cells is an effective method for inducing ICD. ADC-induced ICD provides the "target" and initial signal for the immune system to attack, while PD-1/PD-L1 inhibitors (such as pembrolizumab) remove the "brake" on T cells. When the two are combined, they form a positive feedback loop of "direct killing + immune activation + inhibition relief", which results in excellent therapeutic effects against tumors. The outstanding results of the global Phase III clinical trial EV-302 where the combined treatment significantly prolonged survival are the strongest evidence of this synergy [10].

2.1.3. Activation of Innate Immune Signaling Pathways

Emerging studies have shown that certain targeted strategies can specifically activate innate immune pathways such as cGAS-STING. For instance, precise and targeted photodynamic therapy can cause DNA damage in the tumor cell nucleus and release it into the cytoplasm, strongly activating the cGAS-STING pathway and inducing the production of type I interferons, thereby transforming "cold tumors" of bladder cancer (with few immune cells) into "hot tumors" (with immune cell infiltration), laying the foundation for combined immunotherapy [2].

2.2. Immunotherapy: Amplifier and Memory Formulator

The core function of immune checkpoint inhibitors is to remove the inhibitory effect on the activity of T cells. Under normal circumstances, the PD-1/PD-L1 axis protects the tissues from being attacked by the immune system. However, under pathological conditions, such as in the tumor microenvironment, it is induced by factors like IFN-γ. PD-L1 is highly expressed in cancer cells, causing some immune cells in the body to become inactive, achieving immune escape. This is accomplished by binding to PD-1 on the cells within the patient's body [5]. When targeted drugs enhance the recognition of tumor cells through the aforementioned mechanisms and facilitate the breaking of the "signal shielding" set up by tumors, PD-1/PD-L1 inhibitors can cut off the "immune braking" signal transmission of tumor cells, enabling these activated T cells to continuously exert their killing function and eliminate the remaining bladder cancer tumor cells. More importantly, the activated immune system can generate memory T cells, establishing long-term immune surveillance.

This not only enhances the patient's immunity but also may achieve long-term control of the disease and even clinical cure, which is a goal that purely targeted therapy cannot reach [11].

3. Comprehensive Clinical Evidence of The Combined Strategy of Targeted Therapy and Immunotherapy

The clarification of the collaborative mechanism has facilitated the clinical exploration of various combined strategies, and some of these approaches have achieved revolutionary results and have even rewritten the treatment guidelines [11].

3.1. Antibody-Drug Conjugates (ADC) Combined with Immune Checkpoint Inhibitors: The Current Standard Approach

ADC drugs possess both the targeting properties of antibodies and the toxicity of cell-based drugs. When used in combination with immune checkpoint inhibitors, they demonstrate remarkable efficacy. Antibody-conjugated drugs (ADCs) are complex drugs formed by linking antibodies (or antibody fragments) with chemical drugs, featuring targeted delivery and high efficacy with low toxicity.

3.2. Immune Checkpoint Inhibitors Combined with Chemotherapy and Other Immunomodulatory Agents

Currently, there are roughly three directions for immune combination therapy: immune combined with chemotherapy, immune combined with cytokines, and dual immune combination. In the future, all three of these directions may be developed. A relatively optimal treatment plan will be adopted based on the specific condition of each patient.

3.2.1. Immunotherapy Combined with Chemotherapy

By adding pembrolizumab to the traditional neoadjuvant chemotherapy (such as the dose-intensive MVAC regimen), the chemotherapy exposure target and the immune-activating force work together to enhance the therapeutic effect. This approach is being explored for the treatment of muscle-invasive bladder cancer with non-urinary tract histological variations. Preliminary studies have demonstrated its feasibility [7].

3.2.2. Immunotherapy Combined with Cytokines

Based on the crucial role of IL-15 in activating NK cells and T cells, its super agonist (such as N-803) has been approved for use in combination with Bacillus Calmette-Guérin (BCG) to treat non-muscle-invasive bladder cancer that does not respond to BCG.IL-15 itself is a type of cytokine (a protein that transmits information in the immune system), which can stimulate the proliferation and activation of key immune cells (such as CD8+ T cells and NK cells). IL-15Rα is a part of the receptor for IL-15. When the two combine to form the "IL-15/IL-15Rα complex", it can more stably and efficiently transmit the signal to the immune cells, significantly enhancing their activation effect [4]. Previous research has even attempted to utilize engineered attenuated Salmonella (VNP20009) to deliver the IL-15/IL-15Rα complex locally to tumors, making it safer and more efficient in regulating the tumor microenvironment [4]. This reconfiguration enhances the direct attacking ability of the immune system of body against bladder cancer, achieving the effect of inhibiting tumor growth and even eliminating the tumors.

3.2.3. Dual Immune Combination

Nivolumab blocks the PD-1 pathway. This is initiated by cancer cells when immune cells reach the interior of the tumor and are preparing to attack. Ipilimumab blocks the CTLA-4 pathway. This primarily functions in the early stage of activation of immune cells and operates within the lymph nodes.The early research on the use of nivolumab (anti-PD-1) combined with ipilimumab (anti-CTLA-4) for neoadjuvant treatment of muscle-invasive bladder cancer also demonstrated a high rate of pathological remission, providing more options for bladder cancer patients [3].

3.3. The Synergistic Combination of Emerging Physical/Chemical Methods and Immunology

New therapeutic approaches can actively activate the immune system to attack tumors. When combined with immune checkpoint inhibitors that relieve immune suppression, they are expected to exert a synergistic and enhancing effect, and this is the direction for future exploration [2, 3].

4. Prospects of Combining Future Targeted Therapy with Immunotherapy

Going beyond the current empirical combinations, based on a deep understanding of drug resistance mechanisms such as targeting senescent cells [12], regulating specific metabolic pathways, design more intelligent combination strategies.

Based on multi-dimensional information such as the patient's genome, transcriptome, and microenvironment characteristics, a personalized combination treatment package of "ADC + immunotherapy + (targeted/chemotherapy/physical therapy)" is tailored for the patient.

Applying the successful combined therapy to neoadjuvant, adjuvant, and radical treatment of high-risk non-muscle-invasive bladder cancer, aiming for the highest possible disease cure rate.

Adaptive clinical trial designs such as umbrella and basket designs are widely adopted to efficiently validate combined treatment regimens guided by multiple biomarkers, accelerating the clinical translation of new strategies [3].

5. Conclusion

The combination of targeted therapy and immunotherapy marks that the treatment of bladder cancer has officially entered the era of synergistic and enhanced efficacy in precision medicine. Based on a profound understanding of the tumor microenvironment and the clinical success of the EV+P regimen, this strategy has brought substantial survival improvements to patients with bladder cancer at all stages. Currently, the research focus in this field is shifting from proving the effectiveness of the combination therapy to how to optimize the treatment outcome, screen patients, manage toxicity, and ultimately achieve individualized treatment. Facing numerous challenges such as the complexity of drug resistance mechanisms and the lack of adequate biomarkers, in the future, we must rely on continuous breakthroughs in basic research and continuous innovation in clinical practice. With the continuous deepening of our understanding of bladder cancer biology, as well as the emergence of more new drugs and technologies, a new era of more precise, more effective and more personalized combined treatment for bladder cancer is approaching.

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