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Advances in Immunotherapy and Vaccine for Prostate Cancer

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Abstract

Prostate cancer is one of the most common malignant tumors of the urinary system. The incidence of prostate cancer is high in the elderly male patients, which seriously threatens the life and health. In recent years, immunotherapy to activate anti-cancer host immune cells to kill tumors has become a new area of research for the treatment of prostate cancer. As an important component of immunotherapy, cancer vaccines have a unique position in the precise treatment of malignant tumors. There are many types of prostate cancer vaccines, including monocyte vaccines, dendritic cell vaccines, viral vaccines, peptide vaccines, and DNA/mRNA vaccines, etc. As the most important cancer vaccine based on monocytes, it is the only prostate cancer therapeutic vaccine approved by the US Food and Drug Administration at present, which plays an extremely important role in the immunotherapy of prostate cancer. However, due to its own limitations, Sipuleucel-T has not been widely adopted. Currently, the complexity of immunotherapy and the specificity of prostate cancer mean that other prostate cancer vaccines have not shown expected clinical benefits in large randomized phase II and III trials, and further in-depth studies are still needed.

Key words prostate cancer, cancer vaccine, sipuleucel-T, immunotherapy

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Introduction

Prostate cancer rates have been on the rise in recent years. In 2020, prostate cancer remains the most common malignancy among men worldwide. In China, prostate cancer has become an important factor in threatening the life safety of men [1, 2]. Global Cancer statistics and Chinese Cancer statistics [3-5] show that in recent years, prostate cancer rates continue to rise. Currently, most men with advanced prostate cancer develop castration-resistant prostate cancer(CRPC) [6]. How to further improve the efficacy of CRPC while reducing adverse reactions, has become a focus in this field. In the past decades, immunotherapy has been used to treat prostate cancer through anti-tumor effects driven by immune response. It has brought new immunotherapeutic opportunities. Sipuleucel-T is strongly supported by the U.S. Food and Drug Administration for the treatment of CRPC and has shown promising results. Pembrolizumab has become an important therapeutic tool for prostate cancer immunotherapy [7, 8]. Cancer vaccines use tumor cell-associated antigens to induce a specific anti-tumor immune response that is durable and robust. As an important part of immunotherapy, cancer vaccines have unique and significant advantages against prostate cancer, including monocyte vaccines and dendritic cells,accines, viral vaccines, peptide vaccines and DNA/mRNA vaccines [9]. Among them, Sipuleucel-T plays a great role in promoting prostate cancer immunotherapy. Therefore, this article reviews the latest progress on prostate cancer vaccine, especially Sipuleucel-T vaccine based on mononuclear cells.

Figure 1 shows that general view of vaccine for prostate cancer.

Monocyte-based vaccines

Sipuleucel-T

Sipuleucel-T (Provenge®, Dendreon, USA) is an active immune cell-based immunotherapy that induces an immune response against prostate acid phosphatase (PAP). Prostate acid phosphatase (PAP) is expressed in approximately 95% of prostate cancers and is mainly limited to prostate tissue, which is a target for prostate cancer tumor vaccine development. It is a type of autocellular immunotherapeutic vaccine, composed of peripheral mononuclear cells. Sipuleucel-T consists of autologous peripheral blood mononuclear cells including antigen presenting cells (APCs). Peripheral blood mononuclear cells from patients were obtained by a standard procedure of leukocyte separation approximately 3 days prior to infusion. To increase the immune response to PAP, it is activated by adding PAP and the recombinant fusion protein of immune activator GM-CSF (PAP-GM-CSF) at a specific stage of cell culture. The active components of Sipuleucel-T are autologous APCs and PAP-GM-CSF, in addition to T cells, B cells, natural killer cells, and other cells that specifically bind to PAP expressed in prostate cancer tissue to kill tumor cells. The technology causes patients' own immune system to respond to prostate cancer. In 2010, the US Food and Drug Administration (FDA) approved it into the clinic, and it is the only cell active immune product licensed to treat asymptomatic or mild CRPC [10, 11]. The patient's peripheral blood mononuclear cells (PBMC) rich in antigen-presenting cells (APC) were collected by leukapheresis. After incubating with PA2024 in vitro, the activated cells were injected a new APC, which elicits an antitumor immune response. Among them, PA2024 is the carboxyterminal terminus of PAP and the granulocyte-macrophage colony-stimulating factor (GM-CSF). The amino terminal of GM-CSF was linked to the recombinant protein (PAP-GMCSF). The whole procedure, including leukapheresis, cell activation and reinfusion, repeated every 2 weeks for a total of 3 times (weeks 0, 2 and 4) [12].

IMPACT(NCT00065442) phase III randomized, double-blind, placebo clinical trial [13], where 512 patients were randomly assigned to receive Sipuleucel-T or placebo (2:1). After a median follow-up of 34.1 months, the results showed that: Compared with placebo group (121 patients, 70.8%), Sipuleucel-T group (210 patients, 61.6%) had a 22% relative reduction in the risk of death, and the adjusted hazard ratio for death was 0.78 (95%CI: 0.61-0.98, P=0.03). The median overall survival (OS) was improved by 4.1 months (25.8 months vs 21.7 months). The estimated 36-month survival rate was 31.7% (vs. 23.0% with placebo); In another exploratory study, baseline PSA was found to be a predictor of Sipuleucel-T efficacy [14]. In this study, all patients were divided into four groups on average, with 128 patients in each group. Baseline PSA values (ng/ml) were ≤ 22.1, > 22.1-50.1, > 50.1-134.1, and > 134.1, respectively. The group with the best Sipuleucel-T efficacy was the group with the lowest PSA interval. The median OS in the treatment and control groups was 41.3 and 28.3 months, respectively, while the median OS in the treatment and control groups for the highest PSA interval was 18.4 and 15.6 months.. The study concluded that while Sipuleucel-T is effective in all patients, it is most effective in patients predicted to have a lower risk of progression, so the earlier Sipuleucel-T is used, the better is the treatment response. Sipuleucel-T can only be used by the patient. Before infusion, the patient's identity must be confirmed to match that marked on the infusion bag. When given 3 times, about 2 weeks apart from each treatment, OS of patients with advanced prostate cancer can be significantly improved and the average survival time can be extended by more than 4 months. The most common adverse events (incidence ≥15%) included chills, fatigue, fever, back pain, nausea, joint pain, and headache. Sipuleucel-T was well tolerated, and the most common adverse events were fever and influenza-like symptoms. However, it is worth noting that there was no significant difference in progression-free survival (PFS) or prostate specific antigen (PSA) decline between the two groups. Less than 3% of Sipuleucel-T patients had a PSA decline of 50% or more. Based on the IMPACT [13], D9901 (NCT00005947) [15], D9902A(NCT01133704) [16], double-blind, controlled, multicenter phase III randomized trials, in April 2010, the FDA officially approved Sipuleucel-T as the first prostate cancer vaccine for the treatment of asymptomatic or mildly symptomatic mCRPC [8]. The clinical use of this drug has greatly promoted the development of cancer vaccines, but unfortunately, prostate cancer vaccines other than Sipuleucel-T have not shown promising clinical benefit in large, randomized phase II and III trials.

Immunologic Mechanism of Action of Sipuleucel-T

The immune response induced by Sipuleucel-T is multifaceted, and APC-mediated immune response is the basis of its action, that is, it induces the body to produce PAP specific T cells and B cells, thereby activating the body's immune response to prostate cancer and generating an anticancer effect. The specific mechanisms of sipuleucel-T are as follows: 1) APC activation and immune enhancement. Increased cumulative APC activation, a measure of product potency and immune activation, was statistically significantly associated with improved OS. Sipuleucel-T infusions at weeks 2 and 4 resulted in increased APC activation. This indicates that the first infusion (week 0) primes the immune system and subsequent treatments enhance the immune response. Meanwhile, APC activation is more effective in patients with early prostate cancer [17]. 2) Generate specific immune responses against PAP and PA2024. 3) Antigen diffusion. After an initial immune response to a specific target antigen, Sipuleucel-T expands its response to other antigens expressed by the tumor, which is known as antigen diffusion. In this process, tumor cells lysed by antigen-specific T cells release additional tumor-associated antigens (TAA), which are eventually expressed by the tumor-
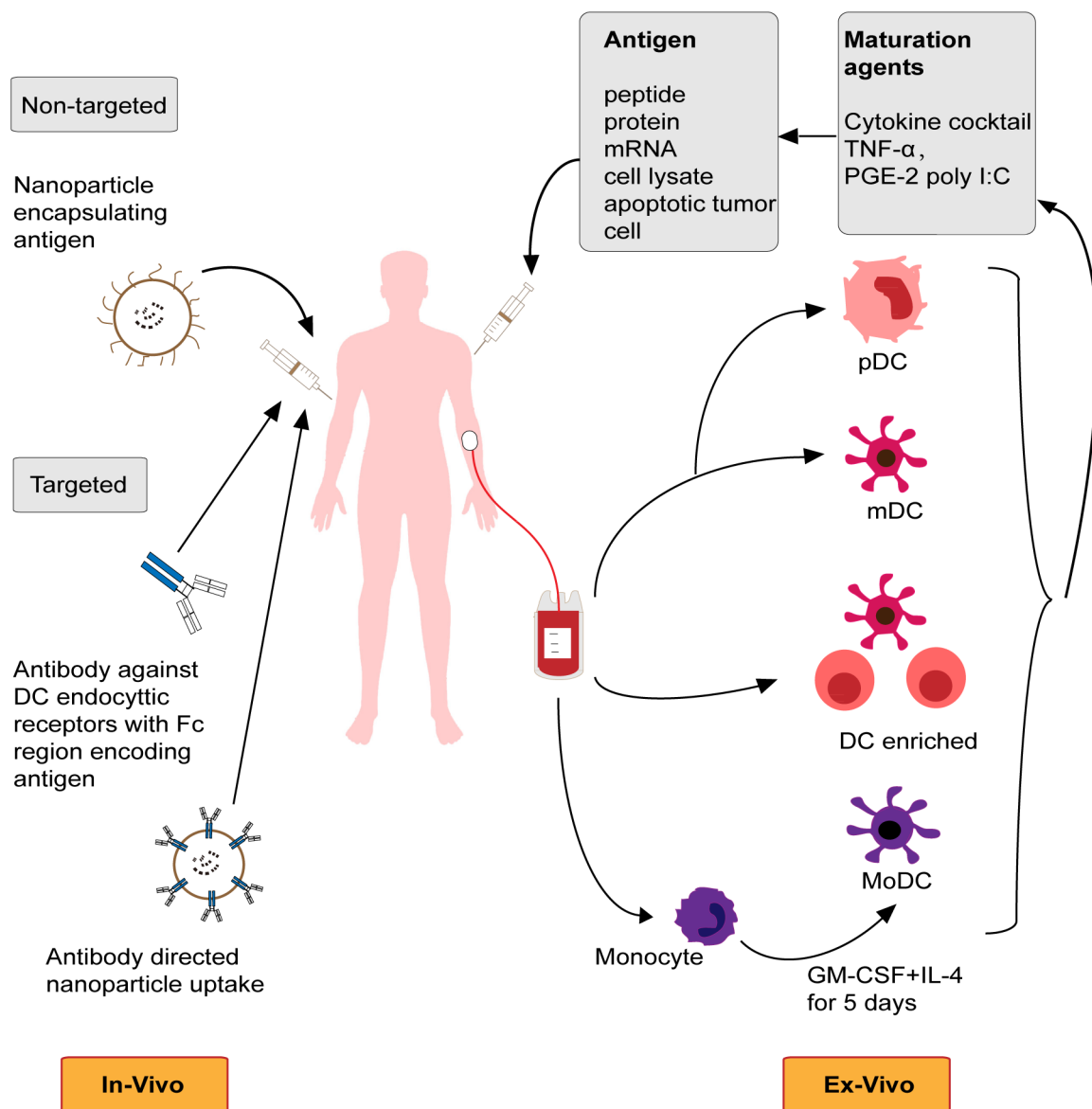
Figure 1. General view of vaccine for prostate cancer (DC, dendritic cell).

associated antigens. APC processing and presentation to induce B cells and T cells to produce immune responses against secondary antigens (such as E-RAS, KLK2, K-RAS, LGALS3 and LGALS8, etc.), which are closely related to the improved survival benefits of Sipuleucel-T [18, 19]. 4) T cell reactive transfer and cytotoxic T lymphocyte (CTL) activity. Fong et al.[20] pointed out that neoadjuvant Sipuleucel-T could induce systemic antigen-specific T cell response and activation effect before radical prostatectomy.

T cells should be recruited to the prostate tumor microenvironment to enhance the immune effect. Antonarakis et al. [21] measured the expression of CD107a on CD8+ T cells specific for PAP or PA2024 and demonstrated that Sipuleucel-T could generate antigen-specific CTL responses in prostate cancer patients. The study found that this response was associated with improved OS after Sipuleucel-T treatment. Kibel et al. [22] documented the cytolytic activity of CTLS against target cells expressing PAP by video, demonstrating tumor induction by antigen-specific CD8+ cells, where tumor lysis is an important part of the mechanism of action of Sipuleucel-T. At the same time, Sipuleucel-T treatment alters the B cell receptor repertoire and

induces the development of long-term immune memory in the organism, making it more useful for killing tumors [23].

Clinical application of Sipuleucel-T

Efficacy evaluation. The IMPACT study [13] showed that Sipuleucel-T could prolong the median OS of mCRPC patients. Schellhammer et al. [14] pointed out that PSA was a strong predictor of Sipuleucel-T treatment response (P<0.0001), and with the decrease of baseline PSA, Sipuleucel-T treatment response would be greater. The hazard ratio for OS was 0.51(95% CI: 0.31-0.85) in patients with baseline PSA $\leq$ 22.1 ng/mL and 0.84 (95%CI: 0.31-0.85) in patients with PSA >134 ng/mL. (0.55 to 1.29), indicating a benefit of Sipuleucel-T at an earlier stage of cancer. Early use of Sipuleucel-T has less tumor immunosuppression and more APC activation, which is more conducive to the long-term stimulation of immune response and long-term clinical benefit. Another notable clinical feature of Sipuleucel-T is the delayed effect, in which proximal end points such as PSA levels, objective disease progression, and the occurrence of disease-related pain

are not altered. In contrast, there was an improvement in the distal end points [24]. Small et al. [25] found that Sipuleucel-T treatment was not associated with time to disease-related pain (TDRP) (HR=0.819, 95% CI: 0.616-1.089, P=0.170), which was associated with delayed time to first use of opioid analgesics (TFOA) (HR=0.755, 95%CI: 0.579-0.985, P=0.038). These changes in late outcomes may be related to the time required to exert the immune antitumor effect after Sipuleucel-T treatment. Sipuleucel-T results were also variable in different ethnic groups.

The PROCEED study [26] showed that compared with whites, African Americans had a higher median OS after Sipuleucel-T treatment (HR= 0.81, 95%CI: 0.68-0.97, P=0.03). This may be related to the differences in the immune system between different ethical backgrounds [27].

The value of drug combinations. Prostate cancer has a low mutation burden and a small number of tumor infiltrating CD8+ T cells, which makes prostate cancer a "cold tumor" of immune response, resulting in a far worse effect of immunotherapy than other solid tumors [28]. Therefore, combination therapy is commonly used in prostate cancer immunotherapy. Theoretically, combination of Sipuleucel-T with the activation and spread of the immune response, combined with the durable efficacy and safety profile, offers the promise of prolonged anticancer activity and is of great value. A randomized phase II open-label trial evaluated Sipuleucel-T versus androgen deprivation therapy (ADT) in the treatment of patients with biochemical recurrence. The results showed that the safety of different administration sequences was good. The PA2024-specific T cell response of Sipuleucel-T first was higher than that of ADT first (P= 0.001), which could induce greater anti-tumor immune response [29]. The results of a mathematical model for Sipuleucel-T and ADT response in prostate cancer developed by Jain et al. [30] showed that 2 doses of vaccine administered before ADT was optimal, reducing cancer mortality by approximately 45% and maximizing median OS. Small et al. [31] randomized phase II trial evaluating Sipuleucel-T combined with abiraterone in the treatment of mCRPC showed that simultaneous administration did not attenuate or change the immune effect of Sipuleucel-T, and the combination was well tolerated. Radiotherapy (hereafter referred to as radiotherapy) and chemotherapy (hereafter referred to as chemotherapy) may synergize with immunotherapy to enhance and expand antitumor immune responses. However, in a randomized phase II trial of Sipuleucel-T combined with radiotherapy, irradiation of up to 30 Gy to a single metastatic site in asymptomatic or minimally symptomatic mCRPC patients did not enhance the immune response associated with Sipuleucel-T treatment [32]. With respect to combination chemotherapy, few studies have been conducted, and two clinical trials evaluating the sequencing of Sipuleucel-T plus docetaxel (NCT02793219 and NCT02793765) were withdrawn with reduction in demand. In addition, a randomized phase II trial of Sipuleucel-T combined with radium 223 in the treatment of bone metastatic mCRPC showed that the combination therapy could improve clinical efficacy, but the immune response was low [33]. Due to the lack of effector T cell infiltration in the tumor microenvironment (TME), the efficacy of immune checkpoint inhibitors (ICI) monotherapy in the treatment of prostate cancer is not good. More recently, Sinha et al. [34] combined Sipuleucel-T and ipilimumab, showing that combination therapy produced modest clinical responses without changing antigen-specific responses. The phase Ib study by Dorff et al. [35] on mCRPC patients who received different sequential regimens of atezolizumab, and Sipuleucel-T showed that the combination therapy was safe and may be more beneficial regardless of the order of administration. At the same time, other emerging therapies, such as the combination of cytokine IL-7, have also achieved encouraging results in phase II trials [36]. Currently,

compared with other immunotherapies, Sipuleucel-T is not widely used, in part because its clinical success rate is limited, and the cost associated with its treatment is not acceptable to most patients. However, the immunologic benefit of Sipuleucel-T in combination therapy still sets the stage for additional large trials.

Clinical limitations "A survey of factors associated with the use of Sipuleucel-T in mCRPC patients in the United States [37] showed that only 730 of 7272 patients treated received Sipuleucel-T, and ethnicity, region of residence, income, and professional recommendation were associated with its use." From a cost perspective, Sipuleucel-T requires three infusions over a period of 1 month. However, the cost-effectiveness analysis for the treatment of mCRPC patients found that the treatment strategy without sipuleucel-T could show the most favorable incremental cost-effectiveness ratios (ICER) [38]. At the same time, the delayed effect of Sipuleucel-T, resulting in the lack of PSA or objective response in clinical trials, affects the assessment of disease progression. Currently, Sipuleucel-T is not widely adopted outside the United States. This drug has been discontinued in Europe because of its complex management, low survival benefit, and high price [39]. Its owner, Dendreon, went bankrupt due to production capacity and financial problems, and was completely acquired by China's Sanpower Group.

Dendritic cell vaccine

DCVAC/PCa vaccine is a PBMC-derived autologous dendritic cell vaccine that can be generated by pulsing PBMC obtained by apheresis with killed prostate cancer cells (LNCaP) followed by subcutaneous injection of mature dendritic cells [40]. Two phase I/II small sample clinical trials [41, 42] have shown that DCVAC/PCa has a good safety profile in the treatment of prostate cancer and can improve the prostate-specific antigen doubling time (PSA). PSADT was significantly prolonged (P<0.001 8). At present, there are few basic and clinical studies on the vaccine. One trial evaluated DCVAC/ PCa combined with first-line chemotherapy (docetaxel plus prednisone) in patients with mCRPC. The results of a randomized, double-blind, phase III trial of the safety and efficacy of DCVAC/PCa in combination with a single-line chemotherapy agent [43] showed that DCVAC/ PCA [maintain consistency and define] in combination with a single-line chemotherapy agent did not prolong OS in mCRPC patients (23.9 months vs 24.3 months, HR: Hr: 1.04, 95% CI: 0.90-1.21, P=0.60).

Cancer cell vaccine

The GVAX/PCa vaccine is a genetically transfected cancer cell vaccine in which the tumor cells provide the antigen. The GVAX/PCa vaccine uses LNCaP, and PC-3 cell lines to secrete GM-CSF [44]. A phase I/II trial in patients with hormone-naive prostate cancer and PSA recurrence [45] showed that 76% (16/21) of patients had a significant PSA reduction 20 weeks after the first treatment. Higano et al. [46] showed that the proportion of mCRPC patients who developed antibodies to GVAX increased with increasing doses. These promising results prompted 2 phase III trials. The VITAL-1 trial randomized asymptomatic patients with chemotherapy-naive mCRPC to GVAX or more Cetaxel + prednisone group; The VITAL 2 trial randomly assigned symptomatic patients with chemotherapy-naive mCRPC to GVAX plus docetaxel or docetaxel plus prednisone. It was disappointing that VITAL was stopped early after a preliminary analysis showed a survival advantage for the docetaxel-plus-prednisone group and a disproportionate number of deaths in the GVAX group. Subsequently, the VITAL-1 trial was terminated prematurely due to a possible failure to improve survival [47].

Table 1. Overview of prostate cancer vaccines.

Vaccine	Type	Mechanism of action	Clinical stage	Results	State	Reference
Sipuleucel-T	Monocte vaccine	Immunotherapy based on active immune cells can induce targeting prostatic acid phosphatase prostate acid phosphatase (PAP) anti-tumor immune response.	Stage Ⅲ	Improve median survival Phase 4.1 months	On the market	[7-9], [11-39]
DCVAC/PCa	Dendritic Cellular vaccine	Peripheral blood mononuclear cells (mononuclear cells) obtained by apheresis cell, PBMC) is pulsed with killed prostate cancer cells (LNCaP) and re-skinned mature dendritic cells are injected below to obtain an antitumor immune response.	Stage Ⅲ	Unprolonged patient Median survival	Finished	[40-43]
GVAX/PCa	Cancer cell vaccine	After gene transfection, LNCaP and PC-3 cell lines were used to secrete granulocyte-macrophage factor(granulocyte-macrophage colony-stimulating factor, GM-CSF) to produce an antitumor immune response.	Stage Ⅲ	Unprolonged patient Median survival	Early termination	[44-47]
PROSTVAC (PSA-TRICOM)	Viral vector vaccine	A plasmid with PSA-TRICOM is inserted into a poxvirus. Patients first receive an initial vaccine for recombinant vaccinia (Prostvac-V), followed by multiple booster immunizations with recombinant avian pox (Prostvac-F).	Stage Ⅲ	Unprolonged patient Median survival	Early termination	[48-51]
Adenovirus/PSA	Viral vector vaccine	Adenovirus /PSA can be used to induce an immune response against PSA and target the killing of tumor cells.	Stage Ⅰ / Ⅱ	The vaccine is immunogenic	Be in progress	[52-54]
PPV	Polypeptide vaccine	Will feed specific tumor antigen peptide antigen presenting cells (antigen presenting cell, APC) on the surface of the major histocompatibility complex, forming peptide - MHC - which is complex, so as to stimulate cytotoxic T lymphocyte (cytotoxic T lymphocyte, CTL) response, producing antitumor immunity.	Stage Ⅲ	Unprolonged patient Median survival	Finished	[55, 56]
GX301	Polypeptide vaccine	A vaccine consisting of four telomerase peptides and two immune adjuvants (Montanide ISA-51 and imiquimod).	Stage Ⅱ	The vaccine is immunogenic	Be in progress	[57, 58]
DNA/mRNA vaccine	DNA/mRNA vaccine	DNA vaccine is a closed circular DNA plasmid designed by the target antigen, which encodes the antigen under the action of the powerful promoter of mammals, and improves the immunogenicity through the targeted antigen presentation. mRNA vaccines deliver mRNA sequences that encode protein antigens into the body, causing the body to express the corresponding protein and inducing an immune response against the protein.	Stage Ⅰ / Ⅱ	The vaccine is immunogenic	Be in progress	[59-67]

Viral vaccines

PSA-TRICOM

Psa-tricom (Prostvac) is a viral vector-based vaccine produced by inserting a recombinant plasmid with a PSA transgene into a poxvirus together with a plasmid encoding three viral T-cell costimulatory molecules (TRICOM). Patients first receive primary immunization with recombinant vaccinia (Prostvac-V), followed by multiple booster immunization with recombinant avian pox (Prostvac-F) [48]. TRICOM, which is composed of B7.1, ICAM-1 and LFA-3, is mainly used to improve T cell affinity and increase tumor cell lysis [49]. The results of phase II trial showed that patients receiving Prostvac-V/F had a prolonged median OS of 8.5 months (25.1 months vs 16.6 months), with an estimated hazard ratio of 0.56 (95%CI: 0.37-0.85, P=0.0061) and a 44% reduction in mortality [50]. This result strongly encourages subsequent phase III trials. The development of cancer vaccines has also set off a new climax. However, the subsequent phase III trial showed that there was no difference in OS between Prostvac group, proSTVAC-GM-CSF group and placebo group, and the trial was terminated prematurely [51].

Adenovirus /PSA

Adenoviruses were originally used as vectors for gene therapy. In recent years, with the higher safety and high immunogenicity of genetically modified products and the development of next-generation vectors, their utility as vaccine vectors has been increasing [52]. Animal experiments have shown that adenovirus /PSA (Ad5-PSA) can induce immune response against PSA and target killing tumor cells [53]. A phase I clinical trial showed that the treatment of mCRPC patients with adenovirus /PSA was safe, and most patients could produce anti-PSA T cell responses. However, the current research on this vaccine is still in phase I/II trials with small samples, and there are few related phase III trials [54].

Peptide vaccine

Individualized peptide vaccines

Personalized peptide vaccines (PPV) are tumor vaccines that are produced by selecting individual peptides for vaccination based on individual genetic structure and functional differences. The mechanism of PPV is that the specific tumor antigen peptide is delivered to the major histocompatibility complex (MHC) on the surface of APC, which is degraded into short peptides in APC and forms peptide-MHC-TCR complex, which is recognized by T cells. The corresponding CTL response is stimulated, thereby carrying out anti-tumor immunity [55]. A randomized, double-blind, placebo-controlled phase III trial of PPV in patients with CRPC who progressed after docetaxel chemotherapy [56] showed that PPV did not prolong OS (P=0.77). Subgroup analysis showed that patients with lower percentage of neutrophils or higher percentage of lymphocytes at baseline could benefit from PPV treatment.

GX301

GX301 is a vaccine consisting of four telomerase peptides and two immune adjuvants (Montanide ISA-51 and imiquimod). It was found to be safe and immunogenic in phase I trials [57]. The results of a multicenter, randomized, parallel-group, open-label phase II trial showed that GX301 vaccine was safe and immunogenic in patients with mCRPC, and the immune response rate was related to the number of immunizations, which provided a reference for treatment options in future studies [58].

DNA/mRNA vaccine

DNA vaccines are closed circular DNA plasmids designed using target antigens, encoding antigens under the action of a strong mammalian promoter, and improving immunogenicity through targeted antigen presentation to kill tumor cells. Currently, DNA-based prostate cancer vaccines mainly include vaccines encoding PAP, PSMA, PSA, etc.[59]. A phase I/IIa trial of encoded PAP [60] showed that the vaccine had a good safety profile, with 14% (3/22) of patients producing PAP-specific IFN-γ-secreting CD8+ T cells immediately after treatment. PAP specific CD4+ and/or CD8+ T cell proliferation was observed in 41% (9/22) patients, and the difference in PSADT was statistically significant (P<0.05). Similarly, the safety and efficacy of DNA vaccine encoding PSMA were also confirmed in phase I/II trials, and its PSADT was significantly increased (P=0.0417) [61]. A recent study [62] showed that PSMA or T-cell receptor γ alternate reading frame protein, peptides of TARP, incorporated into spherical nucleic acid (SNA) vaccines with optimized structures, can significantly affect adaptive immune responses to clinically used prostate cancer targets.

This may become a new research direction in the future. The mRNA vaccine is a synthetic protein antigen encoded by the mRNA sequence delivered to the body to cause the body to express the corresponding protein and induce the body to produce an immune response against the protein to achieve the purpose of disease prevention and treatment [63-65]. Among them, safe and efficient delivery system is the core key technology of mRNA vaccine development [66]. Currently, mRNA vaccines for prostate cancer are under development. To address the bottleneck of tumor antigen screening and vaccine candidates, Zheng et al. [67] showed that KLHL17, CPT1B, IQGAP3, LIME1, YJEFN3, KIAA1529, MSH5, and CELSR3 are important markers of prostate adenocarcinoma. Patients with PRAD immune subtype (PIS) 2 and 3 are more suitable for vaccination. The mechanisms of action and study results of these different types of vaccines are shown in **Table 1**.

Concluding Remarks

In recent years, remarkable progress has been made in prostate cancer immunotherapy, and a variety of new therapies have emerged. As the only prostate cancer vaccine that has been used in clinical practice so far, Sipuleucel-T plays a crucial role in promoting the progress of prostate cancer immunotherapy. However, cancer vaccines are limited to their own characteristics and have not shown greater clinical benefits compared with other therapies. Therefore, there is a need to further improve the cancer vaccination strategy, improve the design of Sipuleucel-T, and find evaluation indicators. It is anticipated that with the continuous optimization of Sipuleucel-T, its advantages in the targeted therapy of prostate cancer will become more significant, and more reasonable combination therapy in the future will continue to improve the tumor killing effect of immunotherapy.

Ethical policy

All procedures performed in this study were in accordance with

the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutioalethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

ZW designed the study and was responsible for the writing of the original draft. ZY edited and approved the final manuscript.

Competing interests

All authors declare no competing interests.

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