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A Review of Sipuleucel-T in Combination with Other Therapies for Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

Recent research has expanded the therapeutic landscape for Sipuleucel-T by introducing several combination treatments. These include innovative hormone therapies (enzalutamide and abiraterone), immunomodulatory agents (including IL-15, IL-7, atezolizumab, ipilimumab, and indoximod), DNA vaccines, and radiopharmaceuticals, many of which have demonstrated enhanced clinical outcomes and received approval from the U.S. Food and Drug Administration (FDA). These combination therapies present novel opportunities to enhance patient survival and quality of life. Sipuleucel-T, a significant autologous cell immunotherapy, was approved by the FDA in 2010 for the treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Integration of Sipuleucel-T with other therapeutic modalities holds promise for advancing mCRPC treatment. Nevertheless, the optimal sequencing and combination strategies for Sipuleucel-T with other therapies remain under investigation, with numerous clinical trials currently exploring new treatment paradigms. Incorporation of these therapies, particularly to develop more effective and personalized treatment strategies, necessitates additional research. Future studies should aim to ascertain the optimal timing and sequencing of treatments and to identify biomarkers that can predict treatment responses, thereby enhancing outcomes for patients with mCRPC. This review underscores potential strategies for the integration of Sipuleucel-T with other therapies and examines their therapeutic potential in mCRPC.

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1. Introduction

1.1 Prostate cancer is a global challenge for men's health

Prostate cancer represents a significant global health concern for men, impacting millions annually. Research indicates notable disparities in the incidence and mortality of prostate cancer across different regions and ethnic groups. For instance, men of African descent experience substantially higher incidence and mortality rates compared to other racial groups, potentially due to genetic predispositions, socioeconomic factors, and disparities in access to healthcare resources [1-3]. In Asia, although the incidence of prostate cancer remains lower than in Western countries, there has been an upward trend in recent years. This increase may be attributed to dietary and lifestyle factors, as well as the lack of comprehensive prostate-specific antigen (PSA) screening programs [4, 5]. In South Korea, projections suggest a significant rise in both the incidence and mortality rates of prostate cancer by 2034, particularly among the elderly male population [6]. The incidence and mortality rates of prostate cancer are undergoing changes across Europe. In Spain, for instance, although there has been a marked increase in the incidence rate since 1990, the mortality rate began to decline in 1998. This decline may be attributed to advancements in screening and treatment methodologies [7]. In the United States, prostate cancer ranks as the second leading cause of cancer-related mortality among men, following lung cancer, with notable disparities observed across different ethnic groups. African American men exhibit significantly higher

incidence and mortality rates from prostate cancer compared to other racial groups. The underlying causes of these disparities are complex and multifactorial, encompassing genetic predispositions, socioeconomic factors, healthcare accessibility, and modifiable risk factors such as dietary habits [1].

Metastatic castration-resistant prostate cancer (mCRPC) represents an advanced stage of prostate cancer that typically arises following the failure of treatment for castration-sensitive prostate cancer. The management of mCRPC is inherently complex, necessitating a selection from a variety of therapeutic strategies and pharmacological agents. In recent years, the advent of novel therapeutic agents has substantially expanded the treatment landscape for mCRPC, with significant implications for enhancing patient survival and quality of life. Notably, androgen receptor signaling inhibitors (ARSI), such as enzalutamide and abiraterone, have been extensively utilized in the treatment of mCRPC and have demonstrated survival benefits in numerous clinical trials [8, 9]. Nevertheless, despite their initial efficacy, resistance to these agents frequently develops, rendering mCRPC a challenging disease to manage effectively [10-12]. Secondly, chemotherapeutic agents such as docetaxel and cabazitaxel continue to play a significant role in the management of mCRPC [13, 14]. Despite the potential of increased side effects, chemotherapy remains an effective therapeutic option in certain cases, particularly when alternative treatments have proven unsuccessful. Furthermore, radiopharmaceuticals like radium-223 have been employed in the treatment of mCRPC patients with bone metastases, demonstrating potential for enhanced survival outcomes [15].

1.2 Overview of Sipuleucel-T therapy

Among the approved immunotherapies for mCRPC, Sipuleucel-T stands out as a pivotal autologous cell-based immunotherapy. Approved by the U.S. Food and Drug Administration (FDA) in 2010, Sipuleucel-T is specifically indicated for patients with asymptomatic or minimally symptomatic mCRPC [16, 17]. Its unique mechanism of action involves stimulating the patient's immune system to target prostate cancer cells. This is achieved by culturing the patient's peripheral blood mononuclear cells, including autologous antigen-presenting cells, with a recombinant protein that comprises prostate acid phosphatase and granulocyte-monocyte colony-stimulating factor [16]. The study indicates that Sipuleucel-T may exhibit greater efficacy in patients with mCRPC who present with a lower disease burden. This increased effectiveness is potentially attributable to a more robust immune response and diminished immunosuppressive effects from the tumor. Furthermore, administration of Sipuleucel-T does not preclude the subsequent use of other mCRPC treatments, thereby allowing for its early integration with other therapeutic regimens [18].

Sipuleucel-T represents a pioneering autologous cellular immunotherapy developed for the treatment of mCRPC. The distinctive feature of this therapy lies in its "personalized" approach, whereby immune cells are harvested from the patient's own body, subsequently processed and activated ex vivo, and reintroduced into the patient to elicit an immune response targeting cancer cells. Recent years have witnessed increased interest in the role of prostate acid phosphatase (PAP) within the context of prostate cancer. PAP, a non-specific phosphor-monoesterase predominantly synthesized in prostate epithelial cells, exhibits elevated levels as prostate cancer advances. Historically, PAP served as the primary biochemical diagnostic marker for prostate cancer until it was gradually supplanted by PSA. Nonetheless, PAP retains significant prognostic value in assessing medium-to-high risk prostate cancer and has demonstrated some efficacy in the immunotherapeutic treatment of the disease [19, 20]. Sipuleucel-T represents a cell-based immunotherapeutic vaccine designed for the treatment of prostate cancer. This vaccine is composed of autologous monocytes, which are stimulated and loaded with an immune-stimulating fusion protein of PAP and granulocyte-macrophage colony-stimulating factor (GM-CSF). The selection of an appropriate antigen is crucial for the efficacy of cell-based immunotherapy. The immunogenic properties of PAP, coupled with its elevated expression in tumor cells, render it an optimal target for therapeutic intervention [21-23] . The primary mechanism of action involves recognition and elimination of cancer cells through activation of the patient's immune system, with PAP serving as a pivotal target [17]. Research has demonstrated that Sipuleucel-T extends survival by eliciting an immune response against PAP, particularly through induction of cytotoxic responses in CD8+ T cells. Furthermore, the therapeutic efficacy of Sipuleucel-T is closely associated with the magnitude of the PAP-specific immune response. Sipuleucel-T has been observed to promote proliferation and activation of PAP-specific CD8+ T cells,

with the intensity of this immune response showing a positive correlation with overall patient survival [24]. The persistence and robustness of this immune response are critical determinants of the success of Sipuleucel-T therapy. During Sipuleucel-T therapy, a patient's immune cells are harvested and conjugated with the antigen PA2024 (containing PAP-GM-CSF) *in vitro*. These activated cells are then reintroduced into the patient to enhance the immune response against PAP [24]. In a study, researchers assessed the potential of Sipuleucel-T to induce long-term immune memory by comparing two cohorts of patients with mCRPC. The first cohort consisted of patients who had previously undergone Sipuleucel-T therapy (treatment group), while the second cohort comprised patients who had not received this treatment (initially untreated group). The findings revealed that individuals in the treatment group demonstrated sustained antibody responses and more focused and convergent B-cell receptor (BCR) repertoires prior to re-treatment, in contrast to those in the initially untreated group, with significant differences observed in the V(D)J gene usage. Furthermore, Sipuleucel-T therapy was associated with higher BCR clonal affinity, which correlated with prolonged survival in patients receiving the treatment for the first time. These results indicate that Sipuleucel-T has the capacity to induce long-term immune memory and exert a lasting influence on the B-cell repertoire [25].

2. Sipuleucel-T has been the subject of extensive clinical investigation

In Phase I/II trials, the efficacy and safety of Sipuleucel-T therapy as a monotherapy have been assessed. These studies demonstrated that Sipuleucel-T can activate the patient's immune system, primarily by engaging antigen-presenting cells to enhance the T cell response against cancer cells [26-29]. In a randomized, double-blind, placebo-controlled, multicenter Phase III trial, Sipuleucel-T was shown to significantly prolong median survival in patients with metastatic castration-resistant prostate cancer. Specifically, the median survival in the Sipuleucel-T group was extended by 4.1 months compared to the placebo group (25.8 months versus 21.7 months), with a 36-month survival probability of 31.7% in the Sipuleucel-T group compared to 23.0% in the placebo group [3]. This therapeutic effect was further corroborated by unadjusted Cox models and log-rank tests, indicating a 22% relative reduction in the risk of death for patients receiving Sipuleucel-T [3]. In the Phase III trial D9901, a cohort of 127 men diagnosed with asymptomatic mCRPC, characterized by the expression of PAP, were enrolled. Participants were randomly assigned to two groups in a 2:1 ratio to receive biweekly infusions. The objective of this trial was to assess the efficacy and safety of Sipuleucel-T in this patient population. The findings indicated that treatment with Sipuleucel-T was correlated with a transient elevation in serum eosinophil counts, which reached a peak at six weeks post-treatment and normalized by week fourteen. Notably, 28% (105 out of 377) of the patients receiving Sipuleucel-T exhibited this eosinophilic increase, which was linked to an enhanced immune response and prolonged prostate cancer-specific survival [30]. Furthermore, although the D9902A trial did not demonstrate a significant difference in the time to disease progression, overall survival was superior in the Sipuleucel-T cohort compared to the placebo group. These findings imply that Sipuleucel-T, as an immunotherapeutic strategy, has the potential to extend survival without markedly impacting the time to disease progression [31].

Sipuleucel-T represents a novel therapeutic approach by leveraging the patient's immune system to combat cancer, rather than exerting a direct cytotoxic effect on tumor cells. The therapeutic procedures involve extraction of antigen-presenting cells from the patient, which are subsequently cultured *in vitro* with recombinant fusion protein PAP-GM-CSF and reintroduced into the patient as activated cells. While Sipuleucel-T has demonstrated a statistically significant extension in overall survival, it has not shown a corresponding significant improvement in progression-free survival [17, 32]. Furthermore, the safety profile of Sipuleucel-T is well-established, with most patients in clinical trials experiencing mild to moderate adverse events. Commonly reported adverse events include infusion-related reactions such as chills and fever, typically manifesting within the first day post-administration and resolving within two days [31, 33]. This favorable risk-benefit profile renders Sipuleucel-T an appealing therapeutic option, particularly when combined with other, more toxic treatment modalities [34].

3. Combination therapies involving Sipuleucel-T

Combination therapy that incorporates Sipuleucel-T demonstrates significant promise in the treatment of prostate cancer. The integration of immune-based therapies with conventional treatment modalities has shown considerable potential in en-

Table 1. Combination therapy with Sipuleucel-T in mCRPC

Combination Therapy	Type	NCT#	Phase of trial	Number of patients
Hormonal Therapy	Androgen deprivation therapy	NCT01431391	II	68
	Abiraterone acetate plus prednisone	NCT01487863	II	69
	Enzalutamide	NCT01981122	II	52
Immunoactive drugs	IL-7	NCT01881867	II	54
	Atezolizumab	NCT03024216	Ib	37
	Ipilimumab	NCT01804465	II	50
DNA vaccines	pTVG-HP	NCT01706458	pilot trial	18
Radiotherapy	Stereotactic ablative radiotherapy	NCT01818986	II	20
	radium-223	NCT02463799	II	32

hancing therapeutic outcomes. In recent years, approval of immune checkpoint inhibitors (ICIs) for various tumor types has heralded a new era in oncological treatment. These therapies enhance the efficacy of the anti-tumor immune response by modulating both the intensity and duration of the immune system's activity. Nevertheless, the efficacy of immunotherapy as a standalone treatment is limited in certain malignancies, thereby rendering its combination with other therapeutic approaches a viable and strategic option [35] (Table 1). In cancer treatment, the combination of immunotherapy and targeted therapy is also considered an effective strategy to improve therapeutic outcomes. Targeted therapy achieves this by inhibiting tumor growth and maintaining required molecular pathways, while immunotherapy achieves long-term tumor destruction by stimulating the host immune response. Targeted therapy and cytotoxic drugs can also modulate immune responses, which provides the possibility for combining these therapeutic strategies with immunotherapy to improve clinical outcomes [36]. In addition, the combination of immunotherapy with traditional cancer treatments such as chemotherapy and radiotherapy has shown synergistic effects in many studies. Chemotherapy and radiotherapy are thought to enhance the release of tumor antigens, thereby increasing the response rate to immunotherapy. However, cytotoxic chemotherapy and radiotherapy may also damage actively proliferating T cells, so the correct treatment regimen and sequence are still under investigation [37]. Nevertheless, the combination of immunotherapy and standard therapy has shown great potential in cancer treatment. By integrating different therapeutic strategies, the limitations of single-agent therapies can be overcome, thus improving treatment outcomes and providing more effective treatment options for cancer patients [38].

3.1 Sipuleucel-T with hormonal therapy

In conjunction with hormone therapy, Sipuleucel-T demonstrates a distinct mechanism of action. While hormone therapy primarily manages the progression of prostate cancer by inhibiting androgen production or activity, Sipuleucel-T offers supplementary therapeutic advantages by enhancing the immune response. As an autologous cell immunotherapy, Sipuleucel-T has been assessed for its biological activity and clinical efficacy in the treatment of prostate cancer through various studies. In a study investigating the effects of Sipuleucel-T administered sequentially with androgen-deprivation therapy (ADT) in patients with biochemically recurrent prostate cancer, it has been revealed that the Sipuleucel-T→ADT sequence elicited a significantly stronger anti-tumor immune response, with PA2024-specific T cell proliferation responses approximately twice as high at various time points compared to the ADT→-Sipuleucel-T sequence ($P = 0.001$). These findings suggest that the order of administration of Sipuleucel-T relative to ADT may influence clinical outcomes, warranting further investigation to elucidate the independent effects of such treatment sequences [39].

Furthermore, integration of Sipuleucel-T with androgen receptor-targeted therapies, including enzalutamide and abiraterone, has demonstrated potential synergistic effects. Abiraterone, a CYP17A1 inhibitor, is frequently administered alongside prednisone for the treatment of mCRPC. Empirical investigations have indicated that co-administration of Sipuleucel-T and abiraterone can be effectively pro-

vided without compromising the immune response or introducing new safety concerns [40]. Moreover, clinical trials have suggested that this combination may confer a survival benefit, although the outcomes can vary across different studies [41].

In the context of evaluating Sipuleucel-T in conjunction with abiraterone, researchers have also investigated its combination with enzalutamide, an androgen receptor inhibitor. Integration of enzalutamide with Sipuleucel-T is hypothesized to potentially augment the immune response and enhance patient survival [42]. These investigations lay a theoretical foundation for employing Sipuleucel-T alongside other anti-androgen agents and offering new directions for future clinical trials. Despite the general perception that these therapies may exert immunosuppressive effects, preliminary studies indicate that their combination with Sipuleucel-T does not significantly impair immune response generation [43, 44]. Overall, Sipuleucel-T may confer additional survival benefits through distinct mechanisms when combined with hormone therapy. The potential of this combination therapy is under further investigation to optimize its application in the treatment of prostate cancer.

3.2 Sipuleucel-T with other immunoactive drugs

In recent years, researchers have investigated the potential of combining Sipuleucel-T with various immunomodulators to augment its therapeutic efficacy. Among the combinations under study are IL-15, IL-7, atezolizumab, ipilimumab, and indoximod. IL-15, in particular, is a critical cytokine known for its role in enhancing the anti-tumor immune response. Empirical evidence suggests that IL-15 can potentiate anti-tumor immunity by facilitating activation and proliferation of effector lymphocytes. In one study, IL-15 was employed to augment the antitumor activity of Sipuleucel-T, which demonstrated a significant enhancement in the activation and proliferation of $CD8^+$ T cells and natural killer (NK) T cells. This enhancement subsequently increased their cytotoxic effects on prostate tumors [45]. IL-7 is recognized as a cytokine that facilitates expansion of lymphocyte populations and augments immune responses. A particular study demonstrated that a combination of Sipuleucel-T with IL-7 significantly expanded $CD4^+$ and $CD8^+$ T cells, in addition to $CD56^{bright}$ NK cells, while also enhancing antigen-specific humoral and T cell proliferative responses. Notably, patients treated with IL-7 exhibited a substantial increase in antigen-specific T cell proliferative and humoral immune responses [46]. Atezolizumab functions as an immune checkpoint inhibitor, specifically engineered to augment the anti-tumor efficacy of T cells through inhibition of PD-L1. In a particular study, participants were randomly allocated to receive either atezolizumab followed by Sipuleucel-T or the reverse sequence. The findings indicated that this combination therapy was safe and well-tolerated irrespective of the administration order of the drugs. However, additional research is required to substantiate its clinical benefits [47]. Ipilimumab functions as a CTLA-4 inhibitor to augment the immune response by deactivating inhibitory signals in T cells. A study demonstrated that Sipuleucel-T, when used in conjunction with ipilimumab, was deemed safe, with clinical activity observed in certain patients. Nevertheless, due to the potential association of ipilimumab with immune-related adverse events, a thorough evaluation of its safety profile is imperative [48]. Collectively, these studies indicate that the integration of Sipuleucel-T with additional immunomodulators has the potential to augment the immune response via multiple mechanisms, thereby improving therapeutic outcomes in patients with mCRPC. Nonetheless, further clinical trials are required to substantiate the long-term efficacy and safety of these combination therapies.

3.3 Sipuleucel-T with DNA vaccines

DNA vaccines represent a novel immunotherapeutic approach designed to elicit antigen-specific T cell responses against tumor cells. Despite demonstrating limited clinical efficacy as monotherapies, DNA vaccines may enhance anti-tumor responses when used in conjunction with other therapeutic modalities [49]. Research indicates that combining DNA vaccines with immune checkpoint inhibitors can substantially improve tumor control and extend patient survival [50]. The potential synergy between Sipuleucel-T and DNA vaccines is attributed to their complementary mechanisms of action: Sipuleucel-T activates the patient's antigen-presenting cells to augment the immune response, while DNA vaccines further stimulate the immune system by encoding specific tumor antigens. In one study, researchers assessed the augmentation of the PAP -specific immune response when Sipuleucel-T was combined with a DNA vaccine encoding PAP (pTVG-HP). The findings revealed that the combination enhanced the PAP-specific antibody response; however, no significant difference in the T cell response was observed between the two groups. Nevertheless, studies have

shown that combination vaccination can enhance and diversify the anti-tumor immune response in terms of T cell and humoral immunity [51].

3.4 Sipuleucel-T with radiotherapy

Radiation therapy is a prevalent modality in cancer treatment, employing high-energy rays to eradicate malignant cells. Research indicates that integrating Sipuleucel-T with radiotherapy could potentiate the anti-tumor immune response, thereby enhancing therapeutic efficacy. Investigators have combined Sipuleucel-T with stereotactic body radiation therapy (SBRT), demonstrating that this combinatorial approach can elicit a more robust immune response and potentially extend progression-free survival [52]. The hypothesis that the combination of Sipuleucel-T and radium-223 may exhibit enhanced clinical efficacy in patients with asymptomatic bone mCRPC has been substantiated by several studies. In a randomized Phase II clinical trial, researchers investigated whether radium-223 could potentiate the peripheral immune response to Sipuleucel-T. The findings indicated that patients receiving the combination therapy experienced a greater proportion of PSA reductions exceeding 50%, alongside improvements in progression-free survival (PFS) and overall survival (OS), compared to those receiving Sipuleucel-T monotherapy [53]. Furthermore, radium-223, a radiopharmaceutical targeting bone metastases, has demonstrated the ability to prolong survival in mCRPC patients and ameliorate symptomatic bone events, pain, and health-related quality of life associated with the disease [54]. The combination of Sipuleucel-T and radiotherapy has demonstrated favorable safety and tolerability profiles in several clinical trials. In one study, the combination did not result in any serious adverse events, and patients exhibited a significantly enhanced immune response [52]. Despite these promising results, further research is necessary to confirm the clinical efficacy and safety of Sipuleucel-T in conjunction with radiotherapy. Future investigations should consider exploring the use of Sipuleucel-T with various types of radiotherapy and its effectiveness across diverse patient populations.

4. Future directions

Recent approvals of novel pharmacological agents have substantially transformed the therapeutic landscape of prostate cancer. The advent of diverse treatment modalities including hormone therapy, chemotherapy, immunotherapy, bone-targeted agents, radioligand therapy, and targeted therapy, has introduced increased complexity in the management of mCRPC [55]. These innovative therapies not only extend patient survival but also facilitate the potential for personalized treatment approaches.

Immune-based combination therapies hold significant promise in the realm of cancer treatment, particularly in enhancing long-term survival rates and improving treatment outcomes for patients. Nevertheless, despite the potential of these therapies, numerous challenges persist in elucidating their precise mechanisms of action. The complexity of immunotherapy arises from the involvement of multiple cell types and signaling pathways. The successful application of immune checkpoint inhibitors has underscored the pivotal role of the immune system in anti-tumor activity; however, the specific mechanisms underlying these therapies remain incompletely understood [56]. Furthermore, the integration of immunotherapy with other treatment modalities, such as chemotherapy and radiotherapy, further complicates mechanistic investigations, as these combinations may exert synergistic effects through diverse pathways [57]. Secondly, assessing the efficacy of immunotherapy presents significant challenges. Conventional methods for evaluating treatment efficacy may not sufficiently account for the long-term effects and delayed responses associated with immunotherapy. Consequently, novel evaluation criteria and methodologies, such as the immune-related Response Criteria (irRC), are being formulated to more accurately assess the clinical effectiveness of these therapies [58]. Development and validation of biomarkers represent another critical challenge in immunotherapy research. Although several potential biomarkers, such as PD-L1 expression and tumor mutation load, have been identified, their predictive power and clinical applicability require further validation and optimization [59].

Prostate cancer demonstrates a comparatively lower responsiveness to immunotherapy relative to other malignancies due to several underlying factors. Primarily, prostate cancer is classified as an immunologically "cold" tumor, characterized by a tumor microenvironment with insufficient immune cell infiltration, which potentially diminishes the efficacy of immunotherapeutic interventions [60]. Furthermore, prostate cancer cells possess the ability to evade immune system detection through multiple mechanisms, including inhibition of T cell activity and alteration of antigen presentation pathways,

thereby further compromising the effectiveness of immunotherapy [61, 62].

Sipuleucel-T primarily functions by enhancing the patient's immune system to identify and target prostate cancer cells. Empirical evidence indicates that Sipuleucel-T augments the number of activated T cells within the tumor microenvironment and enhances T cell diversity, suggesting its role in facilitating T cell recruitment to prostate tissue [63]. Nevertheless, its impact on delaying disease progression is minimal, complicating the assessment of its clinical efficacy [3]. Application of Sipuleucel-T is constrained by financial and logistical considerations. Economic analyses reveal that the treatment incurs substantial costs, with limited economic benefits at the prevailing price point [64]. Consequently, future research should focus on strategies to reduce treatment costs or identify patient subgroups that may derive greater benefit from this therapy.

Regarding therapeutic strategies, the optimal timing for the administration of Sipuleucel-T remains under investigation. Research indicates that Sipuleucel-T may exhibit enhanced efficacy in patients with mCRPC who present with a lower disease burden, potentially due to a more robust immune response [32]. Furthermore, the administration of Sipuleucel-T does not preclude subsequent treatments for mCRPC, thereby facilitating its integration into comprehensive treatment regimens. Future prospect for Sipuleucel-T involves its application in combination with other therapies and its potential use in patients with earlier stages of prostate cancer. Current studies are examining the synergistic use of Sipuleucel-T with other immunotherapies or conventional treatments to augment its clinical effectiveness [65]. Additionally, innovative vaccine strategies and antigen-loading techniques, such as nanoparticles and antibody-antigen conjugates, are under investigation to enhance the efficacy of Sipuleucel-T [66].

Overall, while Sipuleucel-T demonstrates promise in the management of prostate cancer, its clinical application presents challenges that necessitate further investigation and refinement. Immunotherapy has introduced a novel approach to the treatment of prostate cancer. Nonetheless, it is important to acknowledge its limitations in terms of delaying disease progression, reducing PSA levels, extending survival time, as well as issues related to cost and feasibility. Continued exploration and refinement are necessary to enhance therapeutic outcomes. Currently, a variety of immunotherapeutic strategies are available for prostate cancer; however, persistent efforts are required to advance these approaches into mature and effective treatment modalities. Future research endeavors should focus on evaluating its efficacy across diverse patient populations and exploring synergistic strategies with other therapeutic modalities to enhance its clinical utility.

5. Conclusions

Since the approval of Sipuleucel-T in 2010, substantial advancements have been achieved in the management of mCRPC. Clinical trials involving combination therapies have demonstrated the efficacy of Sipuleucel-T in enhancing overall survival and mitigating symptom-related events. Ongoing clinical trials are investigating novel combination therapies and sequencing strategies to optimize the therapeutic efficacy of Sipuleucel-T. This integration marks a significant advancement in the field and offers a viable treatment option for mCRPC in clinical practice. Immunotherapy is poised to become a primary modality for the treatment of prostate cancer and other malignancies, with future research focusing on precision and personalized treatment approaches.

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