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REVIEW ARTICLE

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Current Update on Prostate Cancer Immunotherapy

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Immunotherapy encompasses a wide array of treatment modalities that utilize our natural defense system to fight against cancer and in recent years has contributed to significant improvement in survival and quality of life in patients. However, its use in prostate cancer has been limited due to low efficacy and lack of effective biomarkers. Prostate cancer's unfavorable tumor microenvironment characterized by T-cell exclusion and expansion of T-reg cells, along with the possible inhibitory effect of androgen deprivation therapy (ADT) on the immune system further explains this poor response to immunotherapy. Here, we review current immunotherapies and ongoing clinical trials as well as potential biomarkers being investigated to predict treatment responses to immunotherapy. Finally, we discuss the conflicting results on the best approach to sequencing immunotherapy in relation to ADT.

Key Words: Prostate cancer, Immunotherapy, Clinical trials

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men and the second most diagnosed disease for men in the United States [1]. Although prostate cancer incidence in South Korea is significantly lower than that in Western countries, the malignancy displays minimal symptoms in the early stages and 33.8% of South Korean patients are diagnosed with at least stage III disease [2]. In contrast to the excellent 5-year survival rate of 100% in localized disease, metastatic prostate cancer has a significantly lower 5-year survival rate of 45.9% [3]. The current mainstay of therapy for advanced and metastatic prostate cancer is androgen deprivation therapy (ADT) but cancer cells eventually escape the androgen dependence and become castration resistant.

Immuno-oncological therapy has transformed cancer care by drastically improving survival outcomes and quality of life [4]. Most notably immune checkpoint inhibitors (ICIs) have changed the treatment paradigm in malignancies such as melanoma and lung cancers [5, 6]. Despite its promising results and recent advancements in some solid cancers, immunotherapy's utility in advanced prostate cancer has been limited [7-10]. Pembrolizumab, an ICI with a tissue-agonostic indication, and sipuleucel-T, an autologous cellular vaccine, remain the only immunotherapeutics that have received approval from the U.S. Food and Drug Administration (FDA) [11, 12]. However, the clinical impact of these agents still remains limited by the high cost and modest improvement in survival.

Herein, we review the conventional and experimental immunotherapeutics in prostate cancer. In addition, cellular mechanism and potential factors that limit immunotherapy

in prostate cancer are discussed. Finally, since ADT is the cornerstone of prostate cancer systemic therapy, we cover conflicting results on how ADT may affect the immune system and question the current standard treatment sequence regarding immunotherapy and ADT.

IMMUNE CHECKPOINT INHIBITORS

Tumor cells evade the body's natural immune response via activation of certain immune checkpoint pathways that typically induce T-cell anergy. ICIs interfere with the T-cell coinhibitory signaling pathways to enhance immune-mediated tumoricidal effect [13]. ICIs have become key players in the treatment of many solid tumors, but their clinical benefits in prostate cancer have been disappointing [14].

(1) Pembrolizumab is an IgG4 monoclonal antibody against programmed cell death protein 1 (PD-1) on lymphocytes and it remains the only ICI with FDA approval for the treatment of prostate cancer. It prevents PD-1-induced self-tolerance and inactivation of lymphocytes. Current National Comprehensive Cancer Network guidelines dictate the usage of pembrolizumab specifically for unresectable or metastatic microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR) gene, or tumor mutational burden (TMB) equal or higher than 10 mutations per megabase (mut/Mb) prostate cancers [15, 16]. Table 1 delineates currently open phase III prostate cancer clinical trials on pembrolizumab—however, 3 out of the 6 trials were discontinued. The KEYLYNK-010 trial combining pembrolizumab to poly ADP-ribose polymerase (PARP) inhibitor olaparib was discontinued due to a higher incidence of serious adverse events without observed benefit in overall survival (OS) or radiographic progression-free survival (PFS) [17]. Likewise, KEYNOTE-921 testing pembrolizumab in combination with chemotherapy failed to show statistically significant improvements [18]. KEYNOTE-991 which compared pembrolizumab with enzalutamide to enzalutamide with placebo in metastatic castration-sensitive prostate cancer will be discontinued after the therapy failed to demonstrate improvements at a planned interim analysis [19]. With these latest updates, KEYNOTE-641 along with KEYNOTE-921, 991 China extension trials are the only phase III trials left, while there is still phase II trial such as KEYNOTE-365 [20, 21].

(2) Ipilimumab is an FDA-approved ICI that targets CTLA-4 but has not been approved for prostate cancer. In 2 recent phase III clinical trials, it failed to improve OS in patients with metastatic castration-resistant prostate cancer (mCRPC) [7, 8]. Currently, there are no phase III trials testing ipilimumab as a monotherapy. However, the NCT03879122 trial is investigating it in combination with nivolumab, as anti-CTLA-4 therapy increases infiltrating T cells and induces interferon-γ which stimulates programmed death ligand-1 (PD-L1) expression [22].

(3) Nivolumab is another anti-PD1 antibody that is cur-

Table 1. Open phase III pembrolizumab trials in prostate cancer

Identifier	Title	Patients	Arms	Enrolled	Estimated completion (month-year)
NCT03834506*	KENOTE-921	NHA-pretreated patients with mCRPC	Experimental: pembrolizumab+docetaxel Comparator: placebo+docetaxel	1,090	Oct-23
NCT03834493	KEYNOTE-641	Patients with mCRPC	Experimental: pembrolizumab+enzalutamide Comparator: placebo+enzalutamide	1,240	Feb-25
NCT04191096*	KEYNOTE-991	mHSPC	Experimental: pembrolizumab+enzalutamide+ADT Comparator: placebo+enzalutamide+ADT	1,232	Sep-26
NCT04934722	KEYNOTE-991 China extension	mHSPC	Experimental: pembrolizumab+enzalutamide+ADT Comparator: placebo+enzalutamide+ADT	186	Jan-28
NCT04907227	KEYNOTE-921 China extension	Enzalutamide or abiraterone-pretreated patients with mCRPC	Experimental: pembrolizumab+docetaxel Comparator: placebo+docetaxel	81	Feb-25
NCT03834519*	KEYLINK-010	Metastatic CRPC	Experimental: pembrolizumab+olaparib Comparator: abiraterone+prednisone or enzalutamide	793	Sep-23

NHA, next generation hormonal agent; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; ADT, androgen deprivation therapy.
*Discontinued trials.

rently being explored, but has not received FDA approval. The STARVE-PC phase II trial demonstrated that nivolumab and ipilimumab immunotherapy for patients with mCRPC disease that expresses the constitutively active androgen receptor (AR) variant AR-V7, had a modest improvement in OS rate, but the effect size was not sufficient for pursuing a phase III trial [23]. A phase II trial CheckMate-650 investigating nivolumab and ipilimumab combination in men with mCRPC disease demonstrated high overall response rates but dosing and scheduling modifications are needed to optimize safety [24]. The ongoing phase III nivolumab trials in prostate cancer are detailed in Table 2. Results from the previous phase II study CheckMate 9KD supported further investigation in the phase III CheckMate-7DX trial which is currently recruiting [25].

(4) Atezolizumab is a PD-L1 inhibitor. Table 3 shows ongoing phase III atezolizumab trials in prostate cancer. CONTACT-02 is still recruiting. IMbassador250 trial results are being reviewed, but the trial failed to show the statistical superiority of atezolizumab over the control. However, in a preplanned subgroup analysis, superior PFS was shown in tumors with high levels of PD-L1 expression or high levels of intratumoral CD8-positive T-cell infiltration [9].

VACCINE-BASED TREATMENTS

Cancer vaccines are a form of active immunotherapy that aims to facilitate the presentation of tumor antigens to the immune system. The proposed prostate cancer's immunosuppressive environment is due in part to the dysfunction of dendritic cells (DCs). Accordingly, DC vaccine therapy has the potential to aid in overcoming the immunosuppressive tumor microenvironment. Currently, sipuleucel-T remains the only vaccine-based therapy with FDA approval for the treatment of prostate cancer. It targets prostatic acid phosphatase and the phase III clinical trial IMPACT (Integrated Model for Patient Care and Clinical Trials) demonstrated that sipuleucel-T had a 22% reduction of relative mortality risk [11]. Since its approval, multiple trials investigating combined immunotherapy have been disappointing [26]. NCT01420965 explored combining pidilizumab, but was terminated early, while NCT01832870 investigated ipilimumab and was terminated without phase I reports. Currently, there is an ongoing phase III trial comparing sipuleucel-T to active surveillance for newly diagnosed localized prostatic cancer (NCT03686683).

No other vaccine treatments have been approved for prostate cancer. VITAL-1 and VITAL-2 were clinical trials with promising results investigating GVAX, a synthesized

Table 2. Open phase III nivolumab trials in prostate cancer

Identifier	Title	Patients	Arms	Enrolled	Estimated completion
NCT04100018	CheckMate 7DX: a Phase 3, randomized, double-blind study of nivolumab or placebo in combination with docetaxel, in men with mCRPC	mCRPC	Experimental: nivolumab+docetaxel+prednisone Comparator: placebo+docetaxel+prednisone	984	Aug-27
NCT03879122	A trial of immunotherapy strategies in metastatic hormone-sensitive prostate cancer	mHSPC	Experimental A: ADT+docetaxel+nivolumab Experimental B: ADT+ipilimumab/docetaxel+nivolumab Comparator: ADT+docetaxel	135	Dec-24

mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer.

Table 3. Open phase III atezolizumab trials

Identifier	Title	Patients	Arms	Enrolled	Estimated completion
NCT04446117	CONTACT-02: a phase 3, randomized, open-label, controlled study of cabozatinib in combination with atezolizumab vs. second NHT in subjects with mCRPC	mCRPC	Experimental: cabozatinib+atezolizumab Comparator: either abiraterone+prednisone or enzalutamide	580	Aug-24
NCT03016312	IMbassador250: a phase 3 study of atezolizumab in combination with enzalutamide in men with mCRPC	mCRPC	Experimental: atezolizumab+enzalutamide Comparator: enzalutamide	771	Feb-23

NHT, ovel hormonal therapy; mCRPC, metastatic castration-resistant prostate cancer.

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vaccine using prostate cancer cell lines LNCaP and PC3 secreting granulocyte-macrophage colony-stimulating factor [27]. However, phase III trials were terminated early due to a lack of improved OS and increased mortality.

PROSTVAC is a viral vector containing the PSA gene and several T-cell costimulatory molecules that were used in several clinical trials. Contrary to the promising results in phase II trials, PROSTVAC demonstrated little to no improvement in OS in patients with mCRPC in phase III clinical trials [28-30]. In addition, a phase II trial tested the benefit of using PROSTVAC earlier in the disease compared to active surveillance (NCT02326805) but failed to elicit favorable results [31].

1. Adoptive Cell Therapy

This immunotherapy isolates and manipulates immune cells to increase their capacity to target cancer cells. Chimeric antigen receptor T (CAR T) cell therapy is a classic example and is extremely effective in the treatments of hematologic malignancies due to improved specificity and targeting [32]. CAR T remains a promising treatment option in mCRPC and in other solid tumors, but the safety profile of the treatment remains to be determined [33].

2. Oncolytic Virus Therapy

Oncolytic virus therapy involves utilizing viral vectors to target oncolytic cells and can potentially aid in counteracting tumor-associated immunosuppression and evasion. Conceptually, it is a relatively new mode of therapy as the virus can replicate in situ to have a direct cytocidal effect [34]. Additionally, because the prostate gland is a nonessential organ, oncolytic viral therapy can be used to completely ablate the gland [34]. Oncolytic viral therapy has largely been explored in combination with ICIs [35]. There are several clinical trials exploring this immunotherapy approach and results have been promising but further investigations to clarify the therapeutic potential in prostate cancer are needed.

BARRIERS TO IMMUNOTHERAPY IN PROSTATE CANCER

Despite these diverse immunotherapy modalities, immunotherapy has not been effective in prostate cancer due to its "cold" immune environment. For a robust antitumor immune response, 3 major steps are required: (1) generation of tumor-reactive T cells, (2) physical interaction between target and effector cells, and (3) a microenvironment permissive to immune effector functions [36]. Prostate cancer often lacks distinct characteristics that prevent a clinically meaningful immune response.

Primarily, the TMB of prostate cancer is typically low, resulting in the inefficient generation of tumor-reactive T cells. TMB is increasingly being proposed as a possible predictive marker of response to immunotherapy in various cancers and is associated with high expression levels of neoantigens which correlates with increased immunogenicity [37]. Prostate cancer cells, compared to other cancers successfully treated with immunotherapy such as melanoma, are typically characterized as having low TMB [38, 39].

Next, immune effector cells may be hampered from directly contacting cancer cells, as prostate cancer is characterized by T-cell exclusion. Furthermore, T cells in the adjacent stroma and benign areas often demonstrate anergic and immunosuppressive phenotype. This in part may be explained by the chronic progressive nature of prostate cancer and its inflammatory microenvironment [36].

Additional cellular mechanisms proposed for how prostate cancer maintains an immunosuppressive environment include fibroblasts, T-reg cells, tumor-associated macrophages, mesenchymal stem cells, and myeloid-derived suppressor cells in the tumor stroma. Collectively, these cells secrete mediators that suppress immune activity [40]. Interestingly, as much as 50% of castration-resistant prostate tumors demonstrate phosphatase with tensin homolog (PTEN) inactivation, a tumor suppressor gene. Loss of PTEN function does not affect tumor growth through the loss of its tumor suppressor function but PTEN loss itself can act as an immunosuppressive event, impairing innate and adaptive immunity [41, 42]. Additionally, prostate cancer often produces high levels of transforming growth factor-β, which has a profound inhibitory effect on immune cells including

natural killer (NK) cells resulting in low NK cell infiltration [43, 44]. Finally, tissue aspirate from prostate cancer revealed an increased number of T-reg cells [45]. Taken together, the unfavorable prostate cancer microenvironment is likely a key factor in limiting the efficacy of immunotherapy.

It should be noted that not only the perturbation of immune effector cells and the unfavorable tumor microenvironment pose formidable challenges to developing effective immunotherapeutics in prostate cancer, but factors such as race and previous use of other therapies also add another layer of complexity in prostate cancer immunotherapy. Asian/Pacific islanders have the highest 5-year survival rate in metastatic prostate cancer compared with other races [46], and African Americans respond better to most systemic therapies than Caucasians [47]. ADT can induce T-cell infiltration into the prostate tumor microenvironment [48]. In addition, enzalutamide-resistant prostate cancer expresses higher levels of PD-1 and PD-L1/2 [49]. Therefore, factors such as ethnicity and previous therapies should be considered in developing a rational strategy for immunotherapy in prostate cancer.

PREDICTIVE MARKERS IN IMMUNOTHERAPY

Because immunotherapy is not effective in unselected metastatic prostate cancer patients, predictive biomarkers are needed to identify patients who will likely benefit from immunotherapy.

1. Programmed Death Ligand-1

PD-L1 is used in other tumors as a biomarker for immunotherapy. In prostate cancers, one study reported that the objective response rate to ICI in PD-L1-positive tumors was 5% and in PD-L1-negative tumors, the rate was 3% [10]. Thus, PD-L1 is not considered a viable biomarker of immunotherapy in metastatic prostate cancer.

2. Deficient Mismatch Repair

Deficient MMR genes may result in the overexpression of a variety of immune transcripts including those associated with T cells such as PD-L1 [50]. Underlying dMMR can cause high variation in microsatellite length (MSI-H). Mutations in these genes code for mutant proteins which potentially act as neoantigens that can be recognized by CD8-positive T cells. dMMR/MSI-H tumors showed high response rates and impressive efficacy with ICI treatment [51, 52]. However, dMMR/MSI-H is relatively uncommon in prostate cancer and is reported to be present in 2.2%–12% [50, 51, 53, 54].

3. High TMB

High TMB showed a favorable response to ICI compared with taxanes alone in metastatic prostate cancer. Patients with TMB of 10 mt/Mb or greater had a significantly longer time to the next treatment and OS [55].

4. DNA Homologous Recombination Repair Gene

Homologous recombination repair gene (HRR) mutation, especially the CDK12 mutation showed a favorable response to ICI. CDK12-mutated prostate cancer is linked to poor prognosis and resistance to PARP inhibition, but increased neoantigen load for intratumoral lymphocyte infiltration opens the door to PD-1 targeted therapy [56]. However, CDK12 mutations occur in 5%–7% of patients with mCRPC [57]. There is currently an ongoing phase 2 clinical trial of nivolumab and ipilimumab combination therapy for prostate cancer patients with CDK12 mutation (NCT03570619).

Collectively, effective prostate cancer immunotherapy will require a panel of biomarkers and genomic determinants to identify patients who will likely respond.

IMMUNOTHERAPY IN RELATION TO ANDROGEN DEPRIVATION THERAPY

ADT forms the basis of systemic therapy for advanced prostate cancer and when we consider integrating immunotherapy for prostate cancer treatment, we must consider the interaction between androgens and the immune system. The immunosuppressive effect of androgens has been observed in both rodent and human studies. Women produce more IgM [58] and there is a strong correlation between androgens and genes involved in lipid metabolism that correlate with low

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virus-neutralizing antibody in men [59]. Although variable in ratio, autoimmune diseases are more prevalent in women compared to men and men show increased susceptibility to nonreproductive cancers [60].

Accordingly, castration may restore some of the suppressed immune function. In animal studies, castrated male mice which resulted in the change of sex hormone levels induced a change in immune responsiveness [61]. Androgen deprivation showed enhanced T-cell function and resulted in complete regeneration of male mouse thymus with the restoration of peripheral T-cell function [62]. Castration may also enhance CD4-mediated immune responses [63] and castration temporarily leads to prostate Th1-type T-cell infiltration [64]. Moreover, androgen blockade could mitigate T-cell recognition tolerance and induce prostate-specific T-cell proliferation [65]. Similar findings have been found in human studies where an increase in circulating T cells were found in elderly males undergoing sex steroid ablation therapy for prostate cancer [62]. A separate study showed that patients developed expansion of naïve T-cell compartment after androgen deprivation, along with an increase in effector-cell response to stimulation and prostate tissue-associated IgG responses [66]. Based on these observations, immunotherapy should be combined with or sequenced following ADT.

Conversely, there is a body of data suggesting that ADT may suppress the immune response. For example, Jiang et al. [67] investigated the correlation between hepatocellular carcinoma and sex and reported that androgens down-regulate PD-L1. Interestingly, the same authors did not detect the same negative correlation between AR and PD-L1 in prostate cancer. A more provocative result was reported by Pu et al. [68] in 2016. The team reported that chemical castration, but not surgical castration, suppressed T-cell response in prostate cancer. Similarly, our group has observed that androgens stimulate the antitumorigenic activity of macrophages [69]. Specifically, androgen was shown to induce M1 polarization while in an isolated system, removal of macrophages following orchiectomy partially reversed castration resistance. Taken together, these observations suggest that the clinical efficacy of immunotherapy may need to be assessed in the context of ADT. Indeed, we have proposed that the optimal treatment sequence for immunotherapy in prostate cancer may be prior to the initiation of ADT. Clinical trials are being developed to assess this concept.

CONCLUSION

Despite the progress in understanding tumor immunology over the last decade, immunotherapy has not shown a meaningful clinical effect in prostate cancer. Additional studies are necessary to clarify the mechanisms underlying the "immune-coldness" of prostate cancer. Since ADT is the foundation of prostate cancer systemic treatment and androgens affect the immune system, future immunotherapy trials in prostate cancer should include a rational strategy to assess the interaction between ADT and immunotherapy.

NOTES

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