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Immunotherapy for Metastatic Prostate Cancer: Immuno-cold or the tip of the iceberg?

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Abstract

Purpose of review: Metastatic castration-resistant prostate cancer (mCRPC) is in critical need of new and innovative treatment strategies. Since the approval of sipuleucel-T, the investigatory climate of prostate cancer immunotherapy has been rapidly evolving with promising developments in vaccine and immune checkpoint therapies.

Recent findings: Sipuleucel-T remains the first and only therapeutic cancer vaccine approved for its survival benefit in mCRPC. Additional cancer vaccines are currently being evaluated, with the most promising being a peptide vaccine encoding prostate surface antigen (PSA), known as PSA-TRICOM. Emerging data supports combinatorial strategies for vaccine therapy and a potential role for implementation in earlier stages of advanced disease. Immune checkpoint therapies have demonstrated limited success in prostate cancer with negative late phase trials for ipilimumab (CTLA-4 inhibitor) monotherapy and discouraging early phase results for PD-1 blockade. Novel immune-modulatory targets and rational combination strategies aim to produce more favorable results. Recent progress has been made to determine biologic predictors for response and toxicity in prostate cancer immunotherapy aiming to improve patient selection and safety.

Summary: Steady progress is anticipated in the field of prostate cancer immunotherapy including ongoing development of novel cancer vaccines, immune checkpoint therapies and combinatorial strategies.

Keywords

Prostate cancer; immunotherapy; cancer vaccine; immune checkpoint therapy

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Conflicts of Interest
None

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is in critical need of new and innovative treatment strategies. While recent advances in immunotherapies have revolutionized the management of many tumor types [1–6], the impact of these therapies on prostate cancer has been less pronounced. A clear response has been observed with respect to cancer vaccine therapy [7,8]; conversely, immune checkpoint therapies have demonstrated limited success to date [9–12]. With ample preclinical data suggesting a promising role for immunotherapies in prostate cancer [13–16], ongoing research is currently underway to improve patient selection and define mechanisms of response [17–20]. Here, we aim to review the current scientific evidence for prostate cancer immunotherapy while providing expert perspective on the future trajectory of this exciting field.

Vaccine Therapy and Prostate Cancer: *Sipuleucel-T*

Sipuleucel-T (Provenge®) is an autologous cellular immunotherapy in which immature antigen presenting cells (APCs) are harvested via leukapheresis. These immature APCs are incubated with a recombinant protein (PAP2024), consisting of prostatic acid phosphatase (PAP), a tumor-associated antigen (TAA) expressed in more than 95% of prostatic adenocarcinomas [21], and granulocyte macrophage colony stimulating factor (GM-CSF), which activates APCs [22]. Seventy-two hours later the activated APCs are infused into the patient; and the entire process is repeated 2 weeks later for a total of 3 doses.

In 2010, the results of the landmark IMPACT trial, which enrolled 512 patients with mCRPC who received either sipuleucel-T or placebo, demonstrated an improvement in median overall survival (OS) for sipuleucel-T (hazard ratio [HR] = 0.78, $P = 0.03$). Interestingly, there was no observed difference in progression free survival (PFS) [7]. Post hoc data analysis of the sipuleucel-T cohort demonstrated significant correlation between OS and markers of immune response including cumulative total nucleated cell count, APC count, CD54 upregulation and adaptive immune response against PA2024 [23].

Given its observed survival benefit and favorable toxicity profile, sipuleucel-T is an attractive option for patients with asymptomatic or minimally symptomatic mCRPC. Nevertheless, full implementation of the 3 dose course is time consuming and requires detailed coordination given the need for leukapheresis and shipment of cellular elements before each dose. Optimal implementation with respect to sequence and combination relative to other therapies such as second generation hormonal therapies, chemotherapies or radium-223 remains unclear and is the topic of several recent early phase studies [24,25] as well as ongoing clinical trials [26,27].

Vaccine Therapy and Prostate Cancer: *PSA-TRICOM (PROSTVAC)*

PSA-TRICOM is a poxvirus-based peptide vaccine encoding prostate specific antigen (PSA) gene and TRICOM (costimulatory molecules B7.1, ICAM-1, and LFA-3). Mechanistically the vaccine aims to infect dendritic cells (DCs) and other APCs inducing presentation of the TAA, PSA, and TRICOM to effector T cells. Dosing schedule entails a subcutaneous injection of a primer vaccine on day 1 followed by booster vaccines on day 14, 28 and

monthly thereafter until disease progression [28,29]. A randomized phase II, placebo-controlled study enrolling 125 patients with mCRPC demonstrated a median OS of 25.1 months in the PSA-TRICOM arm versus 16.6 months in the control arm (HR = 0.56; log-rank $P=0.0061$). Similar to sipuleucel-T, there was no difference in PFS [30]. Serologic analysis in patients receiving PSA-TRICOM demonstrated sound immunologic response with approximately 50% of patients exhibiting a greater than 2-fold increase in PSA-specific T cells. Patients with the greatest immune response demonstrated a trend toward improved survival [31]. A phase III trial investigating the survival impact of PSA-TRICOM is currently underway (PROSPECT; NCT01322490). Assuming favorable results, PSA-TRICOM could be the first FDA approved *in-vivo* tumor vaccine.

Vaccine Therapy and Prostate Cancer: *Rationalizing Discordant OS and PFS*

Failure to observe improvement in PFS despite significant prolongation of OS suggests that sipuleucel-T and PSA-TRICOM alter the long-term course of disease and/or demonstrate delayed anti-tumor response [32,33]. As opposed to rapid tumor cell apoptosis associated with declines in serum PSA levels seen with the use of traditional chemotherapies and hormone modulators, therapeutic vaccines may attenuate tumor cell growth [32,34]. This postulate is supported by the fact PSA doubling time is significantly lengthened with sipuleucel-T in the post-prostatectomy setting [35], and argues for incorporation of tumor vaccines at earlier disease stages. The mechanism also highlights potential for impact on outcomes separate from OS. For example, sipuleucel-T demonstrates benefit over placebo in time to first use of an opioid analgesic for cancer related pain [36].

Immune Checkpoint Therapies and Prostate Cancer: *CTLA-4 Inhibition*

The CD28 receptor is constitutively expressed on the surface of T cells and undergoes activation by binding to B7 ligands (B7-1 and B7-2). This costimulatory pathway is negatively regulated by CTLA-4 which competes with CD28 for B7 binding; thereby, effectively blunting T cell activation [37,38]. Inhibition of CTLA-4 effectively results in enhancement of effector T cell function [37,39,40]. Ipilimumab is a human monoclonal antibody engineered to antagonize CTLA-4. Some of the earliest phase I clinical trials investigating CTLA-4 inhibition were conducted in patients with prostate cancer [41–43], and, to date, two phase III trials have investigated the survival impact of ipilimumab on patients with mCRPC.

The first reported trial enrolled 799 men with mCRPC refractory to docetaxel to receive bone-directed radiotherapy followed by ipilimumab (10 mg/kg) or placebo. Induction dosing was performed every 3 weeks for up to 4 doses with maintenance ipilimumab or placebo provided every 3 months until progression or dose-limiting toxicity. The trial barely failed to meet its primary endpoint of demonstrating an improvement in median OS (11.2 months for ipilimumab versus 10.0 months for placebo; HR = 0.85, $P=0.053$); however, statistically significant superior median PFS was seen (4.0 versus 3.0 months; HR = 0.70; $P<0.0001$). Twenty-six percent of patients receiving ipilimumab experienced grade 3 and 4 toxicities, most commonly diarrhea and fatigue. A preplanned subgroup analysis was conducted and suggested that patients with absence of visceral metastases, low alkaline phosphatase levels

and a hemoglobin concentration of 11 g/dL or higher might be more likely to benefit from ipilimumab [10].

The second reported phase III trial accrued 400 chemotherapy-naïve patients with asymptomatic or minimally symptomatic mCRPC and no known visceral metastases. Equivalent median OS was observed between the two groups – 28.7 months in the ipilimumab arm versus 29.7 months in the placebo arm (HR = 1.11; $P = 0.3667$) with, median PFS again favoring ipilimumab (5.6 months versus 3.8 months; HR = 0.67; 95% confidence interval [0.55 – 0.81]) [12]. Although the primary endpoint of OS was negative in both trials, PFS data and the subgroup analysis in the former study suggest a subset of patients with mCRPC may still benefit from ipilimumab therapy.

Immune Checkpoint Therapies and Prostate Cancer: *PD-1/PD-L1 Inhibition*

PD-1 and its ligand (PD-L1) are two additional immune checkpoints that have been identified as therapeutic targets for immunotherapy. PD-1 is primarily expressed on activated T cells and pro-B cells; whereas, PD-L1 is expressed on T cells, APCs, vascular endothelial cells, stromal cells, and cancer cells [44,45]. The PD-1/PD-L1 complex is associated with the B7–CD28–CTLA-4 family serving as a co-inhibitory signal to safeguard the maintenance of immune tolerance [44]. PD-1/PD-L1 interactions inhibit T cell effector functions through distinct mechanisms compared to CTLA-4 [38,46]. Unfortunately, early phase clinical trials investigating nivolumab (PD-1 blockade) and prostate cancer have demonstrated little success to date. Three phase I dose escalation studies of nivolumab monotherapy, enrolling a total of 27 patients with mCRPC, reported no measurable responses [11,47,48].

Future Directions and Perspectives on Prostate Cancer Immunotherapy: *Vaccine Therapy*

Despite having multiple investigational agents in the research pipeline, a rational approach to the implementation of vaccine therapy is essential to optimizing efficacy in prostate cancer. Clinical data involving several tumor types suggests that cancer vaccines work best early on in the disease course when the extent of tumor burden is limited [49,50]. Primary tumor burden can be proportionally immunosuppressive, as well, suggesting that neoadjuvant mobilization of the immune system may actually improve the clinical efficacy of prostate cancer vaccines [49]. Further supporting this notion, a greater than three-fold increase in CD3+, CD4+/FOXP3- and CD8+ T cells was observed in radical prostatectomy samples of patients receiving pre-operative sipuleucel-T compared to pre-treatment prostate biopsies [51]. For these reasons, additional research into the survival impact of vaccine therapy at earlier stages of metastasis and as a neoadjuvant intervention for locally advanced disease is essential. Unfortunately, clinical trials in early stage prostate cancer require many years to mature given the overall favorable prognosis of the disease. To overcome these challenges, identification of predictors of survival is critical for vaccine clinical trial design and optimal patient care. For example, in patients with mCRPC treated with sipuleucel-T, lower baseline PSA is associated with a greater OS benefit [52].

Additional research into neoantigen-derived vaccine methods is a critical unmet need. To date prostate cancer vaccines have only targeted normal tumor tissue antigens such as PAP,

PSA, PSCA and PSMA. With significant immune tolerance anticipated against these host elements, identification and targeting of specific prostate cancer neoantigens has the potential to improve vaccine specificity and efficacy. The burden of somatic mutations for prostate cancer is well established [53]; with several mutated proteins serving as potential neoantigenic targets: ERG gene fusion product, FOXA1, MLL2, UTX and ASXL1 [54].

Future vaccine research is poised to explore combination strategies in prostate cancer. Demonstrating favorable toxicity (mainly short-lived injection site reaction, pyrexia and fatigue), vaccines are a safe adjunct to chemotherapy [55–57]. In addition, first and second generation androgen deprivation therapies stimulate thymic output of T cells, attenuate immune tolerance and promote T cell trafficking to the prostate [58–61] all of which provide prime rationale for synergy. Early studies combining vaccines with CTLA-4 inhibition have demonstrated relative safety and potential efficacy [62–64]. Finally, therapeutic cancer vaccines may actually enhance PD-L1 expression, effectively augmenting the efficacy of PD-1/PD-L1 inhibition which is of utmost interest in prostate cancer, a tumor type with low levels of PD-L1 expression [49].

Future Directions and Perspectives on Prostate Cancer Immunotherapy: *Immune Checkpoint Therapy*

In spite of prior shortcomings with respect to immune checkpoint therapies [10–12], there still exists sound rationale for future research and optimism regarding checkpoint therapy's eventual impact on disease outcomes. Understanding the mechanisms contributing to failed targeting of CTLA-4 and PD-1/PD-L1 in prostate cancer is imperative to guiding future combination strategies and the identification of novel immunotherapy targets. Recently, it has been shown that following treatment with ipilimumab, there is likely a response of adaptive resistance within the prostate tumor microenvironment, facilitated by upregulation of a number of immune checkpoints, including PD-1, PD-L1 and VISTA [18]. This finding has led to an ongoing multicenter study evaluating the safety and efficacy of nivolumab plus ipilimumab in men with mCRPC (NCT02985957). VISTA targeting is currently under phase I investigation, as well (NCT02671955).

Further exploration of early phase treatment failures involving PD-1 blockade is essential. Lack of antitumor response may be attributed by an imperfect relationship between PD-1/PD-L1 expression levels and PD-1 inhibitor efficacy [38]. This feature draws into question whether or not PD-1/PD-L1 status should be considered a predictive biomarker for response. Nevertheless, the recent observation that enzalutamide resistance is associated with upregulation of PD-L1 on DCs in the peripheral blood and tumor microenvironment does suggest further rationale for a sequential approach [13]. Not surprising, a recent phase II study of pembrolizumab in enzalutamide refractory mCRPC demonstrated a 30% response rate with durability noted up to one year [65]. Research into the optimal timing and combination of CTLA-4 and PD-1/PD-L1 blockade is critical to successful implementation in prostate cancer. Several clinical trials are currently addressing these issues by combining immune checkpoint therapies with cancer vaccines, hormone therapies and chemotherapies.

Novel targets for immune checkpoint modulation have been gaining traction across several tumor types including prostate cancer. Negative regulators such as LAG-3, TIM-3 and

TIGIT down-regulate T cell responses and help facilitate “exhausted” tumor infiltrating lymphocytes [66]. Immune activating targets such as OX-40, CD27 and CD137 have also emerged as potential targets [67–69]. Non-T cell targets including tumor-associated macrophages, myeloid-derived suppressor cells and APCs require additional attention in the pre-clinical and clinical setting; an emerging understanding of prostate cancer immunobiology suggests these cellular elements are vital for tumor immune evasion [70,71].

Finally, immune biomarkers are required to maximize efficacy and reduce toxicity. Thus far, baseline CTLA-4 and PD-1 expression on peripheral blood T cells may predict for response to ipilimumab [72–74]. Additional biomarker candidates must be sought out with longitudinal, biologically detailed clinical studies, as well. Toxicities to immune checkpoint therapies serve as an additional barrier to treatment and a critical area of future research. Clonal expansion of circulating CD8 T cell clones precedes the development of severe immune-related adverse events in prostate cancer patients receiving ipilimumab. In effect, peripheral monitoring of CD8 T cell clones may serve as a means to screen for subclinical toxicity prior to its exacerbation [72]. These promising biomarkers need to be prospectively evaluated using larger patient cohorts.

Conclusion

Prostate cancer demonstrates a rich history of immunotherapy research and development spanning adaptive cellular techniques, vaccines and immune checkpoint modulation. Although groundbreaking developments have remained elusive since the approval of sipuleucel-T, the investigatory climate of prostate cancer immunotherapy is rapidly evolving. We currently sit on the tip of the immunotherapy iceberg with novel vaccines steadily advancing and rational combinatorial strategies for immune checkpoint therapy emerging. The future of immunotherapy in prostate cancer is bound to provide excitement and surprise as we explore predictors of response and mechanisms of resistance further defining the optimal strategy to serve patients within this fascinating treatment paradigm.

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Key Points

- The investigatory climate of prostate cancer immunotherapy has been rapidly evolving with promising developments in vaccine and immune checkpoint therapies.
- Emerging data supports combinatorial strategies for vaccine therapy and a potential role for implementation in earlier stages of advanced disease.
- Novel immune-modulatory targets and an evolving understanding of response/resistance mechanisms aim to improve the impact of immune checkpoint therapy on prostate cancer survival.