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Prostate Cancer Immunotherapy

Kenneth F. May Jr.[1,2,3], **James L. Gulley**[4], **Charles G. Drake**[5], **Glenn Dranoff**[1,2,3], and **Philip W. Kantoff**[1,3]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

[2]Cancer Vaccine Center, Dana-Farber Cancer Institute, Boston, MA

[3]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[4]Clinical Trials Group, Laboratory of Tumor Immunology and Biology, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

[5]Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Department of Urology, James Buchanan Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD

Abstract

The interaction between the immune system and prostate cancer has been an area of research interest for several decades. The recent FDA approval of two first-in-class proof of concept immunotherapies (sipuleucel-T and ipilimumab) has stimulated broader interest in manipulating immunity to fight cancer. In the context of prostate cancer, the immunotherapy strategies that have garnered the most interest are the therapeutic vaccination strategies exemplified by sipuleucel-T and PROSTVAC-VF, and immune checkpoint blockade of CTLA-4 and PD-1. Improved understanding of the immune responses generated by these strategies and development of predictive biomarkers for patient selection will guide rational combinations of these treatments and provide building blocks for future immunotherapies.

Keywords

prostate cancer; immunotherapy; vaccine; immune checkpoint blockade

Background

Decades of intensive investigation have made it increasingly clear that the interplay between immunity and cancer is complex. Both the innate and adaptive arms of the immune system are capable of providing antitumor activity. However, tumors have developed myriad ways to suppress and evade the immune system (1). Moreover, the immune system itself can facilitate tumor development and progression (2). Like most types of cancer, prostate cancer develops in an immune-competent environment. Evidence from animal models and human prostate cancer suggests that despite the presence of immune effector cells that recognize tumor antigens, these cells are actively tolerized and become incapable of mediating tumor destruction (3–8). This may occur through a variety of mechanisms, including the induction of regulatory or suppressor T cells, in some cases converted from the effector T cells

Corresponding author: Kenneth F. May, Jr., MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Smith 353, Boston, MA 02215, phone: (617)632-3779, fax: (617)632-5822, kmay1@partners.org.

themselves (9). Increased numbers of CD4+CD25+ and CD8+Foxp3+ regulatory T cells (Treg) cells have been observed in prostate glands and in the peripheral blood of prostate cancer patients, suggesting an important role for active immune suppression of anti-tumor immunity (10–12). Additionally, various mechanisms of chronic inflammation have been implicated in prostate tumorigenesis (13).

Androgen deprivation therapy (ADT), a mainstay of treatment for both high-risk early prostate cancer and recurrent/metastatic disease, has been shown to alter the immune environment in prostate cancer (14). For example, neoadjuvant ADT of prostate cancer patients results in increased numbers of infiltrating CD4 T cells, CD8 T cells, NK cells and macrophages in prostate tissues (15,16). Mouse models have shown that ADT increases the number of T cells in peripheral lymphoid tissues and prostate glands, enhances T cell proliferation to antigen, and promotes recovery of T and B cell populations following chemotherapy (17), as well as mitigates tolerance of prostate-specific CD4 T cells (4). Furthermore, ADT has also been shown to reverse age-related thymic atrophy in mice, and to restore thymic T cell output in both mice and prostate cancer patients (18).

Given evidence of the presence of immune effector cells reactive to cancer, albeit often held in check by suppressive mechanisms, investigators have sought ways to harness the powerful capabilities of anti-tumor immunity while overcoming immune suppression. Two of the most promising and furthest developed immunotherapeutic approaches are therapeutic vaccination and immune checkpoint blockade (Figure 1). Therapeutic vaccination for cancer aims to prime and direct a nascent immune response against tumor-associated or tissue-specific antigens, such as prostate specific antigen (PSA) or prostatic acid phosphatase (PAP), using a variety of strategies including antigen-presenting cells, genetically-modified tumor cells, viral-based vectors, peptides, and DNA (19). The immune responses induced by vaccination are generally thought to include both the cellular and humoral arms of immunity. Therapeutic cancer vaccination is often enhanced by the co-administration of a cytokine adjuvant such as granulocyte-macrophage colony stimulating factor (GM-CSF), which promotes maturation, activation, proliferation, survival, and expression of major histocompatibility complex and costimulatory molecules by antigen-presenting cells, as well as recruiting granulocytes and boosting overall immune effector function. Certain types of vaccines have also been engineered to express T cell costimulatory molecules, such as B7, ICAM-1, and LFA-3, to boost T cell activation and effector function.

Immune checkpoint blockade is a second promising strategy for reawakening anti-tumor immunity. Immune checkpoints are molecules expressed by previously activated immune cells that serve to inhibit and limit immune responses. Therefore, by blocking immune checkpoint molecules, the hope is to sustain and boost an ongoing immune response against cancer. The most extensively studied immune checkpoint molecule is cytotoxic T lymphocyte antigen-4 (CTLA-4). CTLA-4 is expressed by activated T cells, and is a high affinity receptor for the ligand B7 expressed by antigen presenting cells (APCs). Ligation is thought to deliver an inhibitory signal, in contrast to CD28, the other T cell costimulatory receptor for B7, which mediates an activating signal. CTLA-4 knockout mice develop a fatal multi-organ lymphoproliferative disorder at 3 to 4 weeks of age, underscoring the importance of this molecule in controlling immunity (20,21). CTLA-4 blockade using monoclonal antibodies has augmented anti-tumor immunity in a variety of mouse tumor models, including prostate cancer (22–24). CTLA-4 blockade is thought to act primarily by augmenting effector T cell function, though it may also affect Tregs which also express CTLA-4 (25,26).

Another checkpoint molecule of great interest for immunotherapy is programmed cell death 1 (PD-1) (27). PD-1 is expressed by activated T cells and is considered a marker of T cell

"exhaustion," as engagement by its ligands PDL-1 (also known as B7-H1) and PDL-2 results in T cell inhibition and apoptosis. PD-1 knockout mice exhibit a less dramatic autoimmune phenotype than CTLA-4 knockout mice (28,29). PD-1 blockade with monoclonal antibodies also enhances anti-tumor immunity in mouse models (30,31). Of particular interest is the finding that tumor-infiltrating or peri-tumoral lymphocytes in prostate cancer and melanoma patients express PD-1 (32–34) and have impaired effector function (34). A number of cancers, as well as lymphocytes and APCs in the tumor environment, have also been shown to express ligands for PD-1, which may act to suppress PD-1-expressing T cells (35,36). These data suggest that PD-1 blockade is a promising strategy to reverse this mechanism of effector T cell suppression.

Clinical-Translational Advances

A number of immunotherapy strategies have shown some clinical promise over the past several years (19). Most notable has been FDA approval of the first therapeutic vaccine approved for any type of cancer. Sipuleucel-T (Provenge, Dendreon Corp.) is an autologous vaccine prepared using an individual patient's peripheral blood mononuclear cells (PBMC). PBMC (including antigen presenting cells) are harvested and cultured with a fusion protein consisting of prostatic acid phosphatase (PAP) and GM-CSF for 36–44 hours, and then infused back into the patient. A treatment course consists of vaccination every two weeks for a total of three treatments. The immunologic basis of this vaccine strategy involves the *ex-vivo* maturation and activation of a patient's own APCs in the presence of a tumor-associated antigen PAP, which once infused back into the patient will prime a T cell response against PAP. Efficacy of this vaccination strategy was established with the Phase III IMPACT trial (37). This trial randomized 512 patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC) in a 2:1 fashion to receive either sipuleucel-T or placebo. With a primary endpoint evaluating overall survival, patients treated with sipuleucel-T demonstrated an increased median survival of 25.8 months compared with 21.7 months in placebo-treated patients, resulting in a 22% relative reduction in risk of death (hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; P = 0.03). After correction for subsequent docetaxel use and analysis for a variety of patient characteristics as effect modifiers, the effect of sipuleucel-T was consistently maintained. Adverse events were more prevalent in the sipuleucel-T treated group, but were generally mild and flu-like in nature. Immunologic analysis revealed that significantly more patients treated with sipuleucel-T compared with placebo generated antibody responses and T cell responses against the immunizing antigens, and higher antibody titers against immunizing antigen correlated with longer duration of survival. Interestingly, there was no difference in progression-free survival between groups, a similar finding to that seen in a previous Phase III of sipuleucel-T, where the primary endpoint of progression-free survival was not met, but a secondary endpoint of overall survival showed significant improvement compared with placebo (38).

A second vaccination strategy showing promise is PROSTVAC-VF. PROSTVAC-VF (Bavarian Nordic) is a poxvirus-based vaccine engineered to contain PSA and three immune costimulatory molecules (B7.1, ICAM-1, and LFA-3) within a vaccinia virus or fowlpox virus vector. The vaccine is administered as a vaccinia vector priming immunization, followed by a series of fowlpox vector boosts, all given subcutaneously. GM-CSF is co-administered subcutaneously near the vaccination site (within 5mm) on the day of vaccination and for three consecutive days following. Immunologically, the viral vectors may directly infect antigen-presenting cells, or may infect epithelial cells or fibroblasts at the injection site, leading to cell death, and subsequent uptake of cellular debris along with PSA and costimulatory molecules by antigen-presenting cells. This vaccine has been tested in several Phase II trials, including a randomized Phase II study of 125 patients with

asymptomatic or minimally symptomatic metastatic CRPC (39). Vaccinated patients had an improved 3 year survival and longer median survival compared with empty-vector treated control patients (30% versus 17% and 25.1 months versus 16.6 months, respectively), despite no difference in progression-free survival. This may be due to an eventual sustained reduction in tumor growth rate from an activated immune system as recently suggested (40). Again, side effects were generally mild with this vaccination strategy. In this study, there were no detectable antibody responses to the immunizing antigen PSA, though antibody responses to vector were observed in almost all patients, albeit with no correlation to overall survival. In another smaller non-randomized Phase II study of PROSTVAC-VF, the presence of more robust T cell responses to PSA was associated with a trend towards increased overall survival (41). Of note, vaccinated patients surviving longer than predicted by a standard nomogram had decreased Treg suppressive function, while those surviving less than predicted had increased Treg function. A randomized placebo-controlled multi-center Phase III trial comparing PROSTVAC-VF with or without GM-CSF versus control is planned to begin enrolling in 2011 (ClinicalTrials.gov identifier NCT01322490).

Immune checkpoint inhibition represents another major strategy to augment anti-tumor immunity. Blockade of the immune inhibitory molecule CTLA-4 has been the most extensively studied in a clinical setting. CTLA-4 blockade using the monoclonal antibody ipilimumab (Yervoy, Bristol-Meyers Squibb) is being tested for treatment of variety of malignancies, most prominently in metastatic melanoma, for which FDA-approval was attained in March 2011. Interestingly, in the pivotal Phase III trial of ipilimumab treatment for metastatic melanoma (42), ipilimumab treatment alone resulted in objective clinical responses, often of significant duration, in approximately 11% of patients, something not typically seen with vaccination strategies. Additionally, approximately 60% of patients treated with ipilimumab in this trial developed immune-related adverse reactions such as dermatitis, colitis, hepatitis, and endocrinopathies. These findings suggest that many cancer patients contain populations of tumor-specific T lymphocytes that can be effective at mediating tumor destruction once the “brakes” are released. Ipilimumab has been tested in several Phase I and Phase II clinical trials in metastatic prostate cancer, demonstrating PSA declines and objective responses in some patients (43–46), with similar immune-related adverse reactions to that seen in melanoma patients. Accordingly, ipilumumab is now being investigated in two randomized placebo-controlled Phase III trials for patients with metastatic CRPC, both in the pre-chemotherapy (ClinicalTrials.gov identifier NCT01057810) and post-chemotherapy settings (ClinicalTrials.gov identifierNCT00861614).

A second immune checkpoint pathway of considerable clinical interest is PD-1 and its ligands PDL-1 and PDL-2. Much earlier in clinical testing, PD-1 blockade has shown significant activity against a variety of advanced solid tumors, with less apparent immune-related adverse reactions compared with CTLA-4 blockade. Patients with advanced prostate cancer have been included among those treated in two Phase I trials of a fully human monoclonal anti-PD-1 antibody MDX-1106 (Bristol-Myers Squibb), though no clinical responses have yet been noted in these prostate cancer patients in these trials (47,48).

Different immunotherapeutic strategies impact varying aspects of the immune response. Therefore, the concept of combinatorial immunotherapy has become the new frontier for clinical translation. One example of this combinatorial strategy could employ vaccination in an early metastatic setting with minimal disease burden to prime a nascent immune response. This could be followed by checkpoint blockade either shortly following the vaccination to boost a developing anti-tumor immune response focused towards vaccinated antigens, or later in the setting of progressing disease or increased tumor burden to “rekindle” an immune response that is no longer effective. PROSTVAC-VF with GM-CSF

is currently being studied in combination with ipilimumab to determine if this vaccine/checkpoint blockade strategy potentiates the clinical effect (ClinicalTrials.gov identifier NCT00124670). Additionally, the combination of multiple sites of checkpoint inhibition with both CTLA-4 and PD-1 blockade are being evaluated in a Phase I clinical trial for metastatic melanoma (ClinicalTrials.gov identifier NCT01024231). In light of the immune-modifying effects of ADT, trials are also evaluating the combination of vaccination or checkpoint blockade with ADT. Determining the appropriate timing and sequencing of these various types of treatments presents new challenges for investigators to maximize benefit and minimize toxicities. For example, a small randomized trial suggested that vaccine followed by ADT resulted in improved survival compared with the converse (49).

Of concern when combining immunotherapies is the potential for additive autoimmune toxicities. In a trial combining a therapeutic vaccine followed by CTLA-4 blockade in melanoma patients, fewer side effects were noted than with CTLA-4 blockade alone, suggesting that vaccination prior to checkpoint blockade might actually redirect the immune response towards anti-tumor activity and away from autoimmune damage (50). Pathologic analysis of tumors from these patients treated with vaccination followed by CTLA-4 blockade demonstrated that the degree of tumor necrosis correlated with a predominance of CD8 T cells over Tregs, suggesting that combinatorial immune therapy might help tip the balance towards an anti-tumor effector response. Such immunologic concepts will have to be further developed as more patients are treated with immunotherapies, alone and in combination.

There have been several challenges in the evaluation of the efficacy of immune therapies. One such challenge has been the inability to consistently correlate treatment response to expected immune parameters, such as anti-PSA antibody titers or T cell responses. In the absence of reliable immune parameters for monitoring response, biomarkers are sorely needed to help predict which patients might most benefit from immune modulation and also to help determine which patients might be most susceptible to immune-related adverse reactions. Secondly, clinical benefits derived from immune therapies do not necessarily follow the typical response patterns seen with cytotoxic chemotherapies. Progression-free survival has not been a reliable predictor of overall survival. Indeed, in the cancer vaccine trials of sipuleucel-T (37,38) and PROSTVAC-VF (39), an overall survival benefit was seen with vaccination in the absence of a progression-free survival benefit. This disconnect was also seen in a Phase III trial of ipilimumab in metastatic melanoma (42), where increased overall survival was achieved with ipilimumab despite a relatively low number of objective clinical responses (11%). These observations may in part reflect the time required for an anti-tumor immune response to fully develop, the effect of which might be missed by assessment of progression-free survival and only captured at a later time by an overall survival assessment. Furthermore, traditional RECIST criteria for radiologic evaluation of response can be very misleading with immunotherapy, such that lesions may even increase in size before ultimately regressing, as has been seen particularly in the case of immune checkpoint inhibitory therapies. Biopsies of such lesions suggest that increase in lesion size may be due to lymphocytic infiltration rather than progression of disease (50). In fact, given the frequency of such observations, investigators have proposed an alternative “immune-related response criteria” to supplement RECIST criteria when evaluating the efficacy of immunotherapy (51,52). These examples provide insight into the complexity of immune manipulation and the promise of improving efficacy and reducing adverse reactions as the mechanisms of action underlying these therapies become better elucidated.

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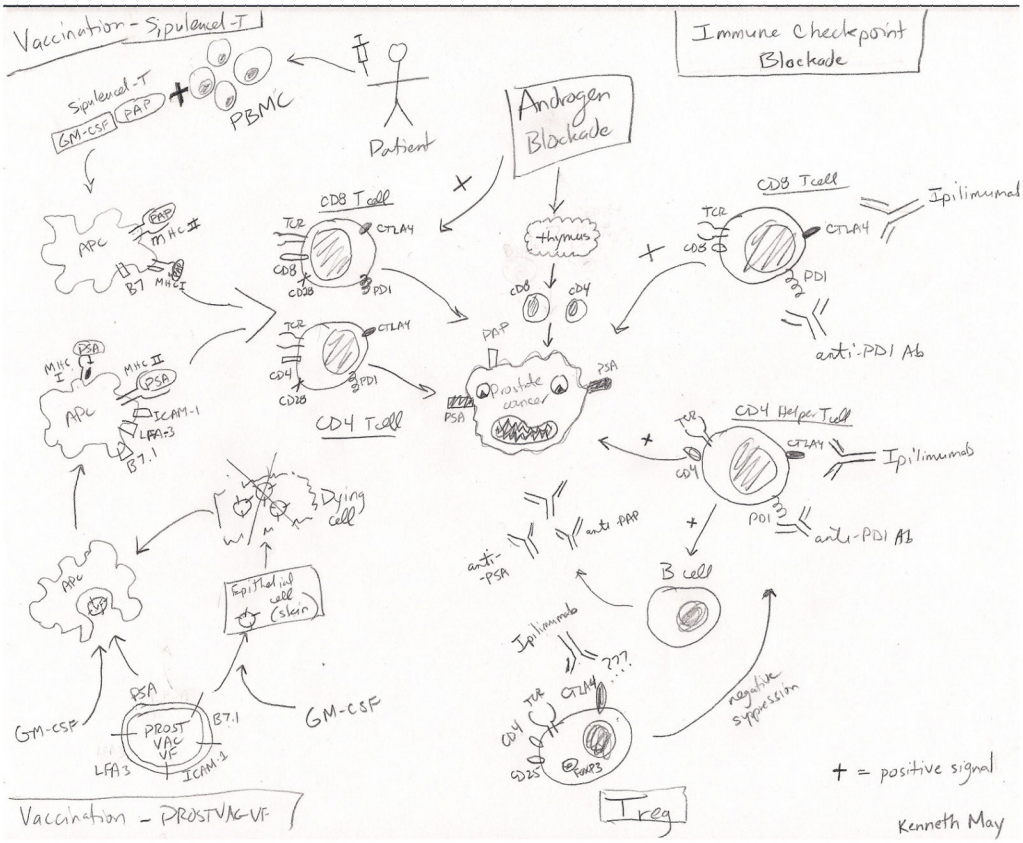

Figure 1.

Immunotherapies augment anti-tumor immunity against prostate cancer. Sipuleucel-T vaccination (Provenge) (upper left corner) is generated by first removing peripheral blood mononuclear cells (PBMC) from the patient via leukopheresis. PBMC including antigen-presenting cells (APC) are incubated *ex vivo* with a fusion protein composed of prostatic acid phosphatase (PAP) and GM-CSF, then re-infused into the patient. Activated APC present the PAP antigen to CD8 and CD4 T cells, causing activation and prostate cancer cytolysis. PROSTVAC-VF vaccination (lower left corner) consists of poxvirus vectors engineered to express PSA antigen and the costimulatory molecules B7.1, ICAM-1, and LFA-3. PROSTVAC-VF vaccinations are given subcutaneously in conjunction with GM-CSF, which either are taken up by skin-resident APC, or infect and lyse skin epithelium or fibroblasts, thereby creating cell debris for APC to ingest. In either case, APC express and present the antigen PSA in conjunction with costimulatory molecules to activate CD8 and CD4 T cells. Immune checkpoint blockade (upper right corner) is illustrated by monoclonal antibody-mediated blockade of CTLA-4 (by ipilimumab) or PD-1 (by anti-PD-1 antibody) expressed by CD8 or CD4 effector T cells. This blockade of inhibitory signals allows for unrestrained T cell attack on cancer cells. CTLA-4 blockade may also affect regulatory T cells (Treg), which also express CTLA-4, though the effect of blockade on this suppressive cell type is less clear. Stimulation of helper CD4 T cells can also subsequently stimulate humoral immunity by B cells secreting natural antibodies to tumor proteins such as PSA and PAP. Androgen ablation enhances T cell anti-tumor immunity by a variety of mechanisms, including increasing prostatic infiltration by T cells, restoring T cell output from the thymus, and mitigation of T cell tolerance.