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Immune Checkpoint Therapies in Prostate Cancer

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Abstract

Advanced prostate cancer is the second leading cause of death from cancer in the United States. In the era of cancer immunotherapy, it was the first malignancy to demonstrate improved survival with a cancer-specific vaccine; thus, proving that prostate cancer is an immune responsive disease. However, the success with immune checkpoint therapies in metastatic prostate cancer has been limited to date with only a subset of patients experiencing clinical benefit. The relative lack of response could be attributed to patient selection based on clinical attributes and the tumor microenvironment. Here, we review the current data on immune checkpoint therapies in prostate cancer and propose future directions.

In recent years, novel strategies of modulating the immune system have resulted in remarkable and prolonged tumor responses in patients with diverse malignancies. Interestingly, the response has not been uniform across all tumors. While the efficacy of vaccine therapies in prostate cancer would argue that it is an immune responsive neoplasm, checkpoint inhibitors have appeared less effective in this disease. Here, we review the available data to contest this impression and propose a path forward.

Regulating T Cell Responses

Much of the focus with cancer immunotherapies has been on modulating T cells, which are present within both normal and malignant prostatic tissue.[1,2] Activation of naïve T cells is tightly regulated and requires the turning on and off of several switches in a timely and coordinated fashion, much like the switches, dials and knobs in an airplane cockpit. To start with, the T cell receptor (TCR) has to engage with its cognate tumor peptide antigens which, for this purpose, must be bound to major histocompatibility complex (MHC) molecules expressed on antigen-presenting cells (APCs). Next, a costimulatory signal must be activated. The best-characterized costimulatory pathway involves members of the CD28/B7 superfamily. The CD28 receptor is constitutively expressed on the surface of T cells, and it interacts with the B7 ligands (B7-1 [CD80] and B7-2 [CD86]) on professional APCs.[3] At the same time, to prevent uncontrolled T cell activity, a number of brakes are in place. For example, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed death-1 (PD-1), other members of the CD28 family also interact with the B7 family of ligands to inhibit T cells responses.[4–6]

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Prostate Cancer is an Immune Responsive Malignancy

Two cancer vaccines targeting prostate tumor-associated antigens have demonstrated an overall survival benefit in randomized controlled clinical trials in men with metastatic castration-resistant prostate cancer (CRPC), testament to the immune responsiveness of the disease. The first to demonstrate efficacy, sipuleucel-T (Provenge) is an autologous dendritic cell (DC) vaccine, which consists of activated DCs engineered to present prostatic acid phosphatase (PAP), a prostate tumor-associated antigen, to tumor-specific T cells. To this end, patient's peripheral blood mononuclear cells (PBMCs) are pulsed with a fusion protein composed of PAP and the DC activating cytokine, granulocyte–macrophage colony-stimulating factor (GM-CSF). The first two randomized trials of sipuleucel-T versus placebo were designed with the primary endpoint of improving time to disease progression.[7,8] Both trials showed that progression-free survival was not different between patients receiving placebo and those receiving sipuleucel-T but the overall survival, a secondary endpoint, was significantly improved by the vaccine. The subsequent Phase III randomized trial was designed with overall survival as the primary end point in patients with asymptomatic or minimally symptomatic metastatic CRPC.[9] This study resulted in a 4.1-month improvement in median overall survival and an improvement in the rate of 3-year survival (31% versus 23%) in the sipuleucel-T arm, with limited toxicity, and led to its FDA approval in 2010. Exploratory analyses since have supported the notion that the greatest benefit from sipuleucel-T is derived by patients with better baseline prognostic factors, particularly those with PSA levels in the lowest quartile, in which the improvement in OS with the treatment was estimated at 13.1 months.[10] More recent studies have confirmed an intratumoral immune effect of the vaccine and immune-parameters associated with outcome in treated patients.[11–14] Together, these studies provided impetus for additional clinical trials in other stages of the disease and in combination with other anti-prostate cancer agents.[15,16]

A second vaccine that has shown a survival advantage in a randomized clinical trials in men with advanced CRPC is PROSTVAC-VF, a vector-based vaccine designed to activate T cell-mediated immune responses to another prostate tumor-associated antigen, PSA.[17] PROSTVAC-VF contains the transgenes for PSA and three T cell costimulatory molecules (TRICOM), consisting of B7-1, leukocyte function-associated antigen-3 (LFA-3), and intercellular adhesion molecule-1 (ICAM-1). An initial injection uses recombinant vaccinia virus as the vector for priming the immune response, and this is followed by multiple booster vaccinations with a recombinant fowlpox vector. The vectors infect APCs, and the PSA together with the T cell costimulatory molecules are expressed on their surface. This allows the APCs to efficiently present the PSA antigen to T cells resulting in antigen-specific tumor killing. In a randomized Phase II study, patients in the PROSTVAC-VF arm compared to the placebo arm achieved an 8.5-month improvement in median overall survival (25.1 months versus 16.6 months) and a 44% reduction in mortality (hazard ratio 0.56). The Phase III trial is completed at this time and awaiting for maturation of the data. Similar to sipuleucel-T, PROSTVAC-VF had no effects on serum PSA levels or tumor volume. These data provide confidence in the immune responsiveness of prostate cancer and open a number of questions, such as when and how these vaccines should be integrated with other prostate cancer therapies. Also, are they exclusive of each other? Or rather, because they build on

different tumor-associated antigens, are they likely to have complimentary effects and perhaps could be sequenced or combined?

Anti-CTLA-4 in Prostate Cancer: When and Who to Treat?

CTLA-4 is an immune checkpoint expressed on T cells, and it serves to constrain T cell-mediated immune responses. Targeting CTLA-4 with a monoclonal antibody (mAb) results in transient enhancement of T cell responses and tumor eradication in preclinical studies.[18] Tremelimumab and ipilimumab are humanized mAbs that target CTLA-4 (anti-CTLA-4). Ipilimumab was the first immune checkpoint agent to be granted FDA-approval, in March 2011, after demonstrating an improvement in the overall survival of patients with metastatic melanoma.[19,20]

In preclinical prostate cancer models, anti-CTLA-4 monotherapy has been largely unsuccessful, but it has been shown to be efficacious when combined with other treatment modalities, including surgery,[21] cryoblation,[22,23] and vaccines,[24,25] as these therapies may enhance tumor antigen release that potentiates the therapeutic effects of anti-CTLA-4. Most clinical trials of ipilimumab in prostate cancer have been conducted in the advanced castration-resistant setting.[26–29] These early clinical studies demonstrated that the minimum effective dose of ipilimumab is 3 mg/kg, that a subset of patients with CRPC clinically benefit from anti-CTLA-4, that ipilimumab can be combined safely with other therapies (e.g., GM-CSF, radiation therapy), and that the adverse events are similar to those observed in other solid malignancies.

More recently, two Phase III randomized trials have compared ipilimumab treatment to placebo in the castration-resistant post-chemotherapy (in combination with a single dose of radiation therapy) and in the pre-chemotherapy settings. In the first, the addition of ipilimumab improved progression-free survival (hazard ratio = 0·70 [95% 0·61–0·82]; p<0·0001 but failed to meet the primary endpoint of improvement in overall survival (hazard ratio = 0·85 [95% CI 0·72–1·00]; p=0·053).[30] A preplanned subgroup analysis suggested, in line with the vaccine data, that patients with favorable prognostic features (absence of visceral metastases, low alkaline phosphatase levels, hemoglobin concentration of 11 g/dL or higher) might be more likely to benefit from ipilimumab. For the subset of patients with these prognostic feature, median overall survival was 22·7 months (95% CI 17·8–28·3) with ipilimumab (n=146) compared with 15·8 months (13·7–19·4) with placebo (n=142; hazard ratio 0·62, [95% CI 0·45–0·86]; p=0·0038).

The second randomized Phase III trial compared the efficacy of ipilimumab (10 mg/kg) to placebo in chemotherapy-naïve metastatic CRPC patients (ClinicalTrials.gov Identifier: NCT01057810). The primary endpoint for this trial is to determine overall survival. The study is designed to detect a 9.3-month median difference (hazard ratio = 0.7) in overall survival with 90% power and 0.05 two-sided significance. The study is completed and is awaiting the maturation of the data.

Anti-CTLA-4 therapy has also been evaluated in two clinical trials in the castration-sensitive prostate cancer setting. In the first trial, tremelimumab plus high-dose bicalutamide, an

androgen receptor antagonist, were given to men with PSA-recurrent prostate cancer.[31] The second trial evaluated ipilimumab in combination with androgen deprivation therapy (e.g., leuprolide, degarelix) in patients with metastatic prostate cancer (Subudhi and Aparicio, submitted). In both trials, examples of prolonged antitumor responses were observed in a subset of patients and thought to be attributable to the anti-CTLA-4 treatment.

At this time, tremelimumab is not FDA-approved for the treatment of any malignancy, whereas, ipilimumab is considered a standard-of-care for only advanced melanoma. The evidence to date supports the notion that a subset of men with advanced prostate cancer derive marked benefit from anti-CTLA-4. Currently, ipilimumab is being tested in combination with other FDA-approved agents for CRPC, including sipuleucel-T (ClinicalTrials.gov Identifier: NCT01804465) and abiraterone acetate plus prednisone (ClinicalTrials.gov Identifier: NCT01688492). The questions now are how to identify those men that derive benefit and what combinations to pursue to improve this efficacy and extend it to those that currently do not appear to benefit.

Anti-PD-1 and Anti-PD-L1 in Prostate Cancer: Is there a role?

The clinical success of anti-CTLA-4 in advanced melanoma led to the development of drugs targeting other immune checkpoints, programmed death-1 (PD-1) and its ligand (PD-L1), which also belong to the CD28/B7 superfamily. Both the PD-1/PD-L1 and CTLA-4/B7 signaling pathways inhibit T cell-mediated immune responses likely through distinct mechanisms.[32–34] This may be attributed to the spatial and temporal expression of PD-L1 on a subset of immune, endothelial and epithelial cells, including cancer epithelial cells; whereas, the B7 ligands are expressed exclusively on immune cells. Blocking the combination of CTLA-4 and PD-1 with mAbs resulted in improved survival in a murine model of melanoma.[35] Surprisingly, in the same study simultaneously targeting all 3 immune checkpoints (CTLA-4, PD-1, and PD-L1) resulted in the best therapeutic outcomes. A plausible explanation is that the ligands, PD-L1 and B7-1, can bidirectionally interact with each other to also inhibit T cell responses.[36] There are currently two mAbs targeting PD-1 that have demonstrated significant therapeutically efficacy in clinical trials. Nivolumab is considered a standard-of-care for the treatment of advanced melanoma,[37,38] non-small cell lung cancer,[39] and renal cell carcinoma;[40] and pembrolizumab has been FDA-approved for the treatment of advanced melanoma and non-small cell lung cancer.[41–43]

In a Phase I trial with nivolumab, none of the 17 patients with metastatic CRPC experienced objective clinical responses;[44] thus, the clinical development of targeting PD-1/PDL-1 as a monotherapy was curtailed. The lack of antitumor responses may be due to a paucity of PD-L1 expression in the prostate tumor microenvironment,[45] as the expression of PD-L1 in tumor tissues has been associated with responsiveness to anti-PD-1/PD-L1 targeting.[44,46] It should be noted that PD-L1 expression in the tumor microenvironment can be a dynamic process. When T cells enter the tumor, there is an upregulation of the immune checkpoints (e.g., CTLA-4 and PD-1), as well as the production of the cytokine, IFN-γ, which leads to upregulation of PD-L1 within the tumor microenvironment.[47] Therefore, therapies such as ipilimumab and sipuleucel-T,[11,48,49] which induce T cell infiltration within the tumor, could

be combined with agents targeting PD-1/PD-L1 to successfully treat advanced prostate cancer.

Clinical Challenges

Monitoring response

A challenge to the clinical development of immune checkpoint therapies is measuring their antitumor effects. In many cases, radiographic responses are delayed or appear after a period of apparent disease progression. This could be attributed to the time required for activated T cells to infiltrate the tumor. Based on the Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria, a subgroup of patients who actually benefited from anti-CTLA-4 therapies were initially classified incorrectly as "non-responders." While the Prostate Cancer Working Group 2 (PCWG2) recommends confirmation of apparent progression on a first imaging study with a second study six or more weeks later,[50] specific immune-related response criteria (irRC) have been developed to prevent premature discontinuation of immune therapies in solid malignancies.[51] Unique to the irRC is the use of overall tumor burden as a measure of disease progression. Under the irRC, new lesions do not represent disease progression if the entire tumor burden is stable or decreases. The irRC also allow for disease progression prior to response by confirmation of progression after first detection. Finally, the irRC classifies durable stable disease as clinical responses. The irRC needs to be prospectively validated in Phase 3 trials. In prostate cancer there is the added complexity of measuring treatment responses in the bone, the predominant site of metastases in this disease. Current imaging modalities have a poor sensitivity and specificity for determining tumor responses. Much research is being put into developing novel functional imaging to address these issues.

Management of adverse side effect in immune checkpoint therapies

Another clinical challenge is that the side-effect profiles for immune checkpoint inhibitors are vastly different from those of standard therapies for solid tumor malignancies. Studies of CTLA-4, PD-1 and PD-L1 inhibition have demonstrated that some patients develop unique toxicities referred to as immune-related adverse events (irAEs)—inflammatory tissue damage caused by activated T cells. Many of these irAEs are transient, suggesting that they are not autoimmune-mediated phenomena, which tend to persist. The safety profile of the immune checkpoint inhibitors in prostate cancer matches that seen in other solid malignancies.[52] The most common toxicities seen with CTLA-4 inhibitors are irAEs that primarily affect the gastrointestinal tract (diarrhea, colitis), skin (rash, dermatitis), liver (transaminitis), or endocrine axis (hypophysitis, thyroiditis). It should be noted that with drugs targeting PD-1/PD-L1 toxicities involving the gastrointestinal tract are less common; however, there is an increase frequency of patients experiencing pneumonitis. Severe irAEs are generally managed with treatment discontinuation and steroid induction, which surprisingly does not appear to affect the therapeutic effects of the immune checkpoint inhibitors. Critical to the use of immune checkpoint inhibitors is the early recognition and treatment of the symptoms irAEs. Early interventions using an established algorithm significantly reduced the frequency of grade 3–4 irAEs in patients treated with ipilimumab in all cancer subtypes. In addition, steroid-sparing regimens (e.g., infliximab) are becoming

incorporated to minimize long-term steroid use. Biomarkers predictive of the onset of toxicities are actively being sought and are needed to allow for prompt clinical intervention for severe irAEs.

Future direction

CTLA-4, PD-1, and PD-L1 are immune checkpoints that have received the most clinical attention at this time, and in the near future clinical trials evaluating the combinations of agents targeting CTLA-4 and the PD-1/PD-L1 pathway will be underway. In addition, large number of additional agonistic and antagonistic mAbs that target immune checkpoints to potentiate T cell-mediated immune response are in various stages of clinical development. These include immune checkpoints such as B7-H3,[53] LAG-3,[54] OX40,[55] and 41BB.[56] Furthermore, there is intense clinical activity in vaccine development and adoptive cell transfer (e.g., chimeric antigen receptor [CAR] T cell) strategies.[57] The challenge ahead is determining optimal patient selection, how to efficiently prioritize the clinical development of these drugs and how to ideally combine them, to conquer each of the lethal malignancies, including prostate cancer.

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