HHS Public Access

Author manuscript

Curr Opin Support Palliat Care. Author manuscript; available in PMC 2021 July 06.

Published in final edited form as:

Curr Opin Support Palliat Care. 2017 September ; 11(3): 225–230. doi:10.1097/SPC.0000000000000278.

Prostate Cancer Immunotherapy: The Path Forward

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Abstract

Purpose of this Review: To provide an overview of current strategies being investigated in the development of immunotherapy in prostate cancer.

Recent findings: Development of immunotherapy in prostate cancer actually began in 2010 with FDA approval of sipuleucel-T. Given that immune checkpoint inhibitor trials have either been negative at the phase 3 level or underwhelming in smaller studies, it is likely that combination strategies will be required to further maximize the impact immune-based therapies on the clinical course of the disease. Emerging data suggests the presence of multiple checkpoint inhibitors in the prostate cancer tumor microenvironment highlighting the need for combination immunotherapy platforms that would potentially include androgen deprivation, chemotherapy or radiation.

Summary:

Pre-clinical and clinical data support immune-based combinations in prostate cancer and several trials are underway to better define the future of immunotherapy in prostate cancer.

Keywords

Prostate Cancer; immunotherapy; Immune Checkpoints; Cancer Vaccines

Introduction

Developing immune based therapeutic strategies for the treatment of cancer is a relatively recent event in the history of medical oncology. This important therapeutic advancement in recent years has largely been driven by immune checkpoint inhibitors. Arguably, the first solid tumor beyond melanoma and kidney cancer to see a significant advancement in modern immunotherapy was prostate cancer in 2010 when sipuleucel-T was approved. Unfortunately, since that landmark phase 3 trial in metastatic castration resistant prostate cancer (mCRPC), immunotherapeutic advances in prostate cancer have been quite limited with no other agents demonstrating positive results in a phase 3 trial. Nonetheless there is reason for optimism as multiple vaccine-based therapies are in late stage testing, and

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Conflicts of Interest:
None

immune checkpoint inhibitors are being evaluated further alone and in combination with other agents. (1)

Sipuleucel-T

Sipuleucel-T is an immunotherapeutic strategy derived from a patient's own immune cells. This vaccine is generated when a patient has their immune cells isolated via peripheral collection using leukapheresis. This collection of cells are then sent to a central processing facility where the immune cells are then exposed to an immune activating cytokine (GM-CSF) linked to the target antigen (prostatic acid phosphatase; PAP). After a 48 hour processing, the immune cells are shipped back to an infusion center where they are reinfused back into the patient. This process is repeated 3 times at 2 week intervals over the course of 1 month to complete the full course of therapy. (2)

After initial clinical trials suggested that sipuleucel-T was well-tolerated and capable of improving survival in men with mCRPC, a phase 3 trial was conducted enrolling 512 patients, randomizing them in 2:1 ratio to treatment with either sipuleucel-T or placebo. (3, 4) (Table 1) Consistent with earlier trials, the treatment was well-tolerated with most frequent side effects including infusion reaction, fever, chills, headache, influenza-like symptoms and myalgias. Also similar to earlier trials, PSA responses were rare and short-term disease progression which was often assessed using PSA parameters did not vary between the 2 randomization groups. Nonetheless, patients treated with sipuleucel-T had a clinically meaningful and statistically significant improvement in overall survival (25.8 vs. 21.7 months; hazard ratio, 0.77; 95% CI, 0.61 to 0.97; P=0.02) with 36-month survival probability also favoring sipuleucel-T (31.7% vs. 23%).(4) The results of this study led to the approval of sipuleucel-T by the United States FDA for the treatment of minimally symptomatic mCRPC.

It is worth noting, that the findings in the sipuleucel-T trial were not universally accepted in the prostate cancer oncology community. Initially when this data was published, there was substantial concern that a therapy that did not decrease serum PSA values or did not change short-term progression could not legitimately extend survival. While these concerns resonated across a medical oncology community that at the time was largely unfamiliar with immunotherapy, subsequent prostate cancer trials and multiple trials with immunotherapies in other cancers have demonstrated similar findings (improved long-term outcomes without short-term improvements in progression). (5) Retrospective data with sipuleucel-T and other immunotherapies have suggested that these treatment strategies may slow progression of disease over time thereby having a lasting antitumor effect that may not be readily apparent initially and may be interpreted as disease progression in the short term. (6–8)

Several years after this controversy began, a neoadjuvant study has provided data suggesting evidence of an immune response after treatment with sipuleucel-T. In this trial 37 evaluable patients with untreated, surgically resectable prostate cancer were treated with sipuleucel-T prior to radical prostatectomy. (9) Peripheral analysis of immune responses demonstrated increased T-cell proliferation and interferon-gamma responses as had been seen in previous studies. When compared with pretreatment biopsies, patients' prostatectomy samples had a greater than 3-fold increase in infiltrating CD4+(FOXP3-) and CD8+ T-cells ($p<0.001$).

Twelve patients used as controls who did not get sipuleucel-T for this study did not have similar evidence of immune infiltration into the prostate. Characterization of the T-cells, which were found primarily at the interface of benign tissue and tumor, were positive for PD1 and Ki67, suggesting an activated state. These data provide pharmacodynamic/immunodynamic evidence that sipuleucel-T can mobilize T-cells against the primary tumor and support the purported mechanism of activity of sipuleucel-t in patients with prostate cancer.

Immune Checkpoint Inhibitors

Shortly after the FDA approval of sipuleucel-T in prostate cancer, another immunotherapeutic agent was approved in metastatic melanoma this time targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The anti-CTLA-4 treatment, ipilimumab, also did not change short-term progression relative to an active control in melanoma patients treated in a phase 3 trial, however it was associated with more partial responses on imaging. (10) Nonetheless, similar to sipuleucel-T, despite the lack of short term changes in disease progression, melanoma patients treated with ipilimumab in this study had a significant improvement in median overall survival. This led to active investigations with ipilimumab in other cancers including prostate cancer where two phase 3 trials were launched, one in chemotherapy naïve mCRPC and the second chemotherapy refractory mCRPC. (Table 1) The latter trial included a combination of ipilimumab with radiation (low dose) serving as an immune stimulating strategy.

The study in chemotherapy refractory patients reported data first and despite advantage modest trend in overall survival in patients receiving ipilimumab and low dose radiation, there was not a statistically significant improvement (median 11.2 vs. 10.0 months; HR= 0.85, p= 0.053). (11) An interesting subgroup analysis done in a post-hoc fashion in this trial suggested that patients with indolent disease, and thus more time to respond to therapy, had better outcomes relative to placebo patients with a similar slower disease courses. This raised hopes for the second study done in chemotherapy naïve patients, where patients would be expected to have more than 2 years to live and thus potentially benefit from the anti-CTLA-4 treatment. The results of this trial, however, were equally disappointing. Despite an apparent improvement in progression free survival (median 5.6 vs. 3.8 months; HR=0.67) and increases in PSA responses (23% vs. 8%) both favoring the ipilimumab treated patients, there was no improvement seen in overall survival (28.7 months for ipilimumab vs. 29.7 months for placebo; HR=1.11, p=0.3667). (12) The negative findings in both trials, along with substantial amount of immune related adverse events seen have tempered the enthusiasm for anti-CTLA-4 targeting as monotherapy in prostate cancer. (11, 12)

Another strategy involving immune checkpoint inhibition is focused on the PD1 interaction with its binding ligand (PDL1) which occurs in the tumor microenvironment. PD1 expression is generally expressed on immune cells while PDL1 may be expressed on tumor cells or other immune cells with immune regulatory function. Through the inhibition of either PD1 or PDL1, immune cells and the tumor microenvironment may be released from inhibitory mechanisms and thereby be able to immunologically kill cancer cells. (13) This

strategy has been remarkably effective in many cancers including melanoma, bladder cancer, renal cancer and lung cancer, however the prevalence of PD1/PDL1 expression in the tumor microenvironment of prostate cancer has been found to be low. (14) For this reason, there has not been as much optimism for this treatment strategy in prostate cancer, however recent data has suggested that the PD1 inhibitor pembrolizumab has been associated with clinical responses in a minority of patients in preliminary data. (15) Especially noteworthy was an antitumor effect that was seen in liver lesions of at least 2 patients. For this reason, investigations of PD1/PDL1 inhibition in prostate cancer, both alone and in combination with other therapies, are ongoing.

Optimal Patients for Immunotherapy

Despite several ongoing phase III trials, there is currently only one FDA approved immune based therapy for prostate cancer and that is sipuleucel-T. (16) Nonetheless, the ideal population for this treatment remains a topic of discussion. (17) This is especially true given the lack of short-term results (i.e. lack of PSA declines) associated with this therapeutic strategy. One analysis associated with the phase 3 trial has suggested that patients with a lower PSA had a greater overall survival benefit than patients with a higher PSA. (18) Patients who had a PSA less than 22.1 ng/ml had a median 13-month improvement in overall survival (41.3 vs. 28.3 months; HR= 0.51) relative to placebo patients. This was contrasted with those who had a PSA greater than 134 ng/ml, where the benefit was considerably less (median 2.8 months; 18.4 vs. 15.6 months; HR= 0.84). There was decreasing benefit with each escalating PSA quartile evaluated in the study with a median 7.1-month improvement for patients with a PSA from 22.1–50.1 and a median 5.4 month improvement for patients with a PSA from 50.1–134 ng/ml.

While PSA is not a surrogate for tumor burden and also can vary substantially between patients with similar tumor burden, the implication of these findings suggest that patients with less tumor volume may benefit most from immunotherapy. (19) These findings complement existing data that suggest that patients with higher tumor burden may have greater immune suppression. (20)

Mechanisms of Immune Resistance

An analysis of patients treated with ipilimumab has brought to light novel mechanism of immune resistance that remind us the immune microenvironment is a dynamic arena where immunotherapeutic actions may lead to compensatory immunoregulatory reactions. In a study in patients with both castration resistant and castration sensitive disease, biopsies were evaluated after treatment with ipilimumab. (21) The tumors were found to have increased expression of PDL1 on CD68+ macrophages after treatment with ipilimumab. While conventional wisdom may suggest these patients should respond to subsequent treatment with an anti-PDL1 inhibitor, a largely separate and distinct subset of CD68+ cells indicated that PDL1 inhibition alone likely would not be effective. In addition to PDL+ CD68+ cells, there also CD68+ cells expressing V-domain Ig suppressor of T cell activation (VISTA), which is another immune inhibitory mechanism, distinct from the PD1/PDL1 axis. (22)

While it remains unclear how effectively VISTA can be targeted as agents are still in early clinical trials/development, it is becoming more clear that the immune equilibrium in the tumor microenvironment is more complicated than just simply PD1/PDL1 inhibition. In reality, other secondary and tertiary resistance mechanisms such as VISTA likely exist within tumors or their microenvironments, thereby creating the need to develop multi-therapeutic immune-based platforms that may have a greater chance of combatting the immunomodulatory compensatory mechanisms that exist, which may attempt to reverse anti-tumor immune responses.

Future Directions: Combination Strategies

Given the biologic complexity that is now becoming apparent as more immunologic investigations are conducted, it has become clear that the initial monotherapy trials developing immunotherapy in prostate cancer and other malignancies represents only the initial foray into immuno-oncology. One strategy which could be developed to mitigate the immune evasiveness of the tumor is combination immune strategies such as combining therapeutic cancer vaccines and immune checkpoint inhibitors. A previous study has suggested that there may be opportunities with such combinations for therapeutic synergy in prostate cancer.

A dose escalation trial combined a therapeutic cancer vaccine prostvac with ipilimumab. (Prostvac is a pox viral based vaccine targeting PSA which has demonstrated preliminary evidence of immunologic and clinical efficacy, and is currently in phase 3 testing in mCRPC.) (19, 23–25) Despite the variable dosing in 30 patients, the median overall survival seen with this combination was 34.4 months, which compared favorably to a relatively contemporary study of prostvac alone where the median overall survival was 26.3 months. (26) Importantly, data from a prognostic nomogram suggests that these patients were relatively equivalent. Although direct comparisons with different studies should be done cautiously, this hypothesis generating data suggests potential synergy between immune checkpoint inhibitors and vaccines. These findings may take on greater meaning in light of the two negative phase 3 studies with ipilimumab in advanced prostate cancer. (11, 12) Toxicity in this study appears largely driven by ipilimumab, but did not seem to be expanded beyond that which would be expected by ipilimumab alone. (26) A current study is evaluating a combination of prostvac, low-dose ipilimumab, and the anti-PD1 inhibitor nivolumab in both mCRPC and in the neoadjuvant setting (NCT02933255).

There is also strong rationale for combination immunotherapy studies involving standard therapies in prostate cancer including docetaxel, androgen deprivation and radiation. (1) While androgen deprivation has been suggested to enhance the immune response by decreasing tolerance and increasing naïve T-cells in the periphery, both of which could enhance a patient’s responsiveness to vaccine-based therapy, chemotherapy and radiation have both demonstrated an ability to immunogenically modify they tumor. (27–30) Preclinical studies with have suggested that MHC-1 and tumor antigen expression are enhanced by chemotherapy (docetaxel) and even low doses of radiation (consistent with alpha or beta particles emitted by radiopharmaceuticals). (27, 29–31) In addition, these levels of radiation have been shown to enhance FAS-ligand expression and antigen-specific

T-cell killing as well, perhaps mediated via FAS ligand. A clinical trial with prostvac and samarium-153 (a beta particle emitting radiopharmaceutical, FDA approved for palliation in patients with metastasis to the bone) improved median time to progression over samarium-153 alone (3.7 vs. 1.7 months; p=0.03; n=44) in late stage (chemotherapy-refractory) mCRPC. (32) Similarly, there is clinical data supporting vaccine and docetaxel from a combination study done in metastatic breast cancer. In this study patients were either randomized to a (MUC1 and CEA targeting) pox viral-based vaccine (PANVAC) with docetaxel and compared to docetaxel alone. Again, patients receiving the vaccine chemotherapy combination had an improved median progression free survival vs. chemotherapy alone (7.9 vs 3.9 months; p<0.001; n=48). (33)

Combining multiple immunotherapies with cytotoxic therapy may be the best way to overcome both tumor heterogeneity and compensatory immune mechanisms. Once the first wave of immunotherapy approvals is complete in the coming years, the hope would be to rationally combine vaccines, multiple checkpoint inhibitors, immunocytokine agents and cytotoxic therapy to optimize in vivo anti-tumor immune responses. (34)

Conclusion

While conventional immunoncology tenets do not put prostate cancer in the same immune responsiveness realm as melanoma or kidney cancer, the FDA approved therapeutic cancer vaccine sipuleucel-T should be a signal that prostate cancer patients can mount immune responses against their tumors. Given that even conventional “immune responsive” tumors still have a minority of patients who respond to approved checkpoint inhibitors, all tumors including prostate cancer may ultimately benefit from combination immunotherapy treatment platforms. Such therapies could bring multiple aspects of the immune system to bear on the tumor (i.e T-cells, NK cells, humoral responses, immunogenic modulation and cytotoxic effects) all of which could contribute substantial improvements in sustained anti-tumor immune responses in advanced disease. Perhaps, similar principles could be applied in localized disease as part of (neo)adjuvant therapy where micrometastatic disease may be more susceptible to immunogenic elimination. Though often forgotten, the modern age of immunotherapy dawned in prostate cancer with the approval of sipuleucel-T and the hope remains that by the time we reach twilight, functional cures will be frequent outcomes for most patients with prostate cancer.

Acknowledgements:

The authors acknowledge the Center for Cancer Research at the National Cancer Institute, NIH for their support.

Financial Support and Sponsorship:

None

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Summary Points

- Sipuleucel-T is an FDA-approved therapeutic cancer vaccine for metastatic prostate cancer which has demonstrated a survival advantage and an ability to mobilize immune cells to the tumor microenvironment in a neoadjuvant trial.
- Two randomized phase III trials with ipilimumab in metastatic prostate cancer have failed to meet their primary endpoint of improved overall survival.
- Studies with anti-PDL1/PD1 treatments have been modest in terms of proportion of patients deriving clinical benefit.
- Correlative clinical data suggest that there are multiple relevant immune checkpoints in the tumor microenvironment.
- Immune-based combinations including, androgen deprivation, chemotherapy and radiation present a rational path forward for therapeutic development in prostate cancer.

Table 1.

Results from Selected Phase 3 Trials of Immunotherapy in Prostate Cancer

Ref	Treatment	Population	n	Results
3	Sipuleucel-T	mCRPC	125	Despite not attaining the primary endpoint (PFS), this study demonstrated a significant improvement in overall survival first suggesting that this treatment may have a survival benefit despite lacking a PFS signal.
3	Sipuleucel-T	mCRPC	98	Discontinued accrual prematurely after initial study did not demonstrate a PFS advantage.
4	Sipuleucel-T	mCRPC	512	Building on the earlier experience, this trial had overall survival as a primary endpoint. Replicating the results of the initial trial, for a second time sipuleucel-T demonstrated an overall survival advantage despite no PFS advantage. (25.8 vs. 21.7 months; HR=0.77, p=0.02) This led to FDA approval.
11	Ipilimumab + low dose Radiation	Docetaxel-treated mCRPC	799	This study in late stage prostate cancer used radiation as an immune adjuvant and demonstrated a trend to improved survival, but fell short of that primary endpoint based on predetermined statistical requirements. (Median 11.2 vs. 10.0 months; HR= 0.85, p= 0.053).
12	Ipilimumab	Docetaxel-naïve mCRPC	602	Despite an advantage in PFS (median 5.6 vs. 3.8 months; HR=0.67), there was no advantage seen in this early stage mCRPC patient population, with survival actually favoring the placebo arm. (28.7 vs. 29.7 months; HR=1.11, p=0.3667).

mCRPC – metastatic castration resistant prostate cancer

PFS – progression free survival