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Demystifying Immunotherapy in Prostate Cancer: Understanding Current and Future Treatment Strategies

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Abstract

Immunotherapy has emerged as a viable therapeutic option for patients with prostate cancer. There are multiple potential strategies that employ the immune system including therapeutic cancer vaccines that are designed to stimulate immune cells to target antigens expressed by cancer cells. Sipuleucel-T is a vaccine currently approved for the treatment of minimally symptomatic metastatic prostate cancer, while the vaccine PSA-TRICOM and the immune checkpoint inhibitor ipilimumab are in phase III testing. Although there are no short term changes in disease progression or available biomarkers to assess response, these agents appear to improve survival. One hypothesis suggests that this apparent paradox can be explained by the growth moderating effects of these treatments which do not cause tumor size to diminish, but rather stall or slow their growth rate over time. For this reason the use of immunotherapy earlier in the disease process is being investigated. Another approach is to block immune regulatory mechanisms mediated by the molecules CTLA-4 and PD-1. Additional future strategies will combine immunotherapy with other standard therapies, potentially enhancing the latter's clinical impact and thereby improving both time to progression and overall survival due to the combined effects of both treatments. Prospective trials are currently evaluating these hypotheses and will ultimately serve to optimize immunotherapy in the treatment of prostate cancer.

Keywords

Immunotherapy; Prostate Cancer; Therapeutic Cancer Vaccines; Immune Checkpoint Inhibitors; Combination Immunotherapy

INTRODUCTION

In recent years, the promise of decades of preclinical research in immunotherapy has begun to be realized in late-stage clinical trials. To the surprise of some, success has occurred in prostate cancer, a disease not previously known for its immunogenicity. There are several possible reasons why prostate cancer has been amenable to immune-based therapies. First, several tumor-associated antigens (TAAs) are overexpressed on prostate cancer cells, including but not limited to, prostate-specific antigen (PSA), prostatic acid phosphatase

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(PAP), and prostate-specific membrane antigen (PSMA).^{1–3} These TAAs can be specifically targeted by activated immune cells, such as cytotoxic T lymphocytes (CTLs) as part of an immune-mediated antitumor response.⁴ A second characteristic of prostate cancer that makes it a good target for immunotherapies is its relatively indolent clinical course. While many metastatic cancers often have survival times measured in months, it is not uncommon for men with metastatic prostate cancer to live several years or more.⁵ This prolonged clinical course potentially allows time for immune-based therapies to generate an antitumor response that can result in improved clinical outcomes. The 2 leading immunotherapy strategies currently being developed in prostate cancer are therapeutic cancer vaccines and immune checkpoint inhibitors. (Table 1)

IMMUNOTHERAPY STRATEGIES

Therapeutic Cancer Vaccines

Therapeutic cancer vaccines are designed to stimulate immune cells to target certain TAAs overexpressed on cancer cells and, notably, they are not associated with significant toxicities. Different strategies are used to generate a targeted antitumor response. Some therapeutic cancer vaccines (hereafter referred to as vaccines) are generated by *ex vivo* cellular processing and activation.⁶ Other vaccines are designed as vectors to deliver an immunostimulatory signal to the immune system via subcutaneous injection, and to activate CTLs *in vivo*.⁷ A less specific immune strategy has been to inject irradiated tumor cells into the patient with the goal of generating an immune response to any of the TAAs expressed on the tumor cells.^{8–9} Although this latter strategy has potential, recent randomized clinical trials employing this approach have failed to yield evidence of clinical benefit.

Immune Checkpoint Inhibitors

Unlike vaccines, which stimulate an immune response by specifically targeting tumor antigens, immune checkpoint inhibitors affect the immune system's ability to auto regulate immune responses.¹⁰ Immune regulatory mechanisms are the body's way of controlling immune responses so that once stimulated, CTLs do not become overzealous and attack the body's healthy structures. A demonstration of the significance of these immune regulatory mechanisms can be seen in CTLA-4 knock-out mice that are missing these immune regulatory mechanisms. These mice die within 2 weeks due to CTL infiltration of organs.¹¹ As a therapeutic strategy, the goal of immune checkpoint inhibitors is to take the “brakes” off the immune system, allowing CTLs to attack cancer cells.¹² Established strategies that target the inhibitory molecule CTLA-4 are associated with a significant number of immune-related adverse events (irAEs), such as dermatitis, colitis and panhypophysitis, which represent collateral damage caused by activated CTLs.^{13–14} Emerging immune checkpoint strategies target other molecules, and preliminary studies suggest that they can establish an immune response with fewer significant irAEs.¹⁵

IMMUNOTHERAPY AGENTS

Sipuleucel-T

Sipuleucel-T is an activated cellular therapy designed to target PAP. The vaccine is generated through *ex vivo* stimulation of antigen presenting cells (APCs) which in turn activate CTLs. A patient's immune cells are collected from peripheral circulation via leukapheresis and transported to a central cellular processing facility. These cells are then exposed for approximately 48 hours to PAP fused to GM-CSF, which is included as an adjuvant for its immunostimulatory properties.^{9, 16} After this process is completed, the immune cells are evaluated for a minimum threshold of CD54 expression, which has been established for the purpose of release criteria to assure product quality. Retrospective data

have suggested that CD54 expression may be associated with clinical outcome, but this has not been prospectively validated as a true surrogate or predictive marker of benefit.¹⁷

Early clinical trials of sipuleucel-T demonstrated safety and suggested efficacy, leading to a pair of small phase III trials.^{18–19} Both of these registration studies were conducted in minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Both trials were set to enroll 125 patients, with time to progression (TTP) as the primary endpoint.²⁰ After the first trial completed accrual (n = 125), it was determined that there was no difference in TTP between the treatment and placebo arms. Shortly thereafter, accrual for the second trial was halted at 98 patients. On long-term follow-up it was determined that patients in the first trial who were treated with sipuleucel-T demonstrated a survival benefit relative to placebo.^{20–21} However, because these data were captured as a secondary endpoint, and because the clinical trials were small in size, they were not sufficient to lead to approval by the United States Food and Drug Administration (FDA).

In order to prospectively evaluate overall survival as a primary endpoint, a third and larger phase III trial was conducted, again in men with asymptomatic or minimally symptomatic mCRPC. This trial enrolled 512 patients, randomizing them 2:1 in favor of sipuleucel-T. Consistent with the earlier trials, there were few declines in PSA and no measurable change in time to first evidence of radiographic or PSA progression (TTP) which was measured for a relatively short time (median of approximately 3.5 months). Nonetheless, patients treated with sipuleucel-T showed significantly improved overall survival compared to patients treated with placebo (25.8 vs. 21.7 months; HR: 0.78, 95% CI, 0.61–0.98).²² Analysis of subgroups of patients showed activation of antigen presenting cells as determined by upregulation of CD54, activation of T cells response to PAP as well as the PAP-GMCSF conjugate as well as an antidody response to PAP as well as the antibody conjugate. Interestingly, the magnitude of the antibody response correlated to overall survival.²² Interestingly, in a retrospective analysis, those with lower PSA levels were more likely to gain benefit than those with a higher PSA. This trial was sufficient to meet the criteria for FDA approval, which was granted in April 2010.²³ Sipuleucel-T is currently indicated for mCRPC patients with minimal or no symptoms. Additional studies have been completed and are ongoing to investigate the potential role of sipuleucel-T for patients with earlier-stage prostate cancer, including those with no radiographic evidence of disease and those with newly diagnosed disease.^{24–25}

Recently a post hoc analysis has raised concerns about the Phase III trial that led to the FDA approval of sipuleucel-T.²⁶ This analysis suggested that leukapheresis in the control arm may have negatively impacted the immune system (presumably leading to infection or cancer progression) leading to poor outcomes in patients younger than 65 years of age. It also was suggested that patients older than 65 years should have lived longer based on subgroup comparisons to other trials. As pointed out by multiple respondents, the comparison of subgroups of patients across multiple trials is inexact and can lead to ambiguous findings.^{27–28} With regard to the concerns about leukapheresis, the potential number of immune cells transiently removed from circulation via this procedure was approximately 1–3% or less of the patient's total lymphocytes and cannot reasonably explain changes in survival. In fact a separate study of over 400 patients undergoing multiple leukapheresis procedures did not show an increase in infections or cancer incidence.²⁸ The critics also suggested that the lymphocytes that were replaced via homeostatic proliferation in response to leukapheresis were less functional, but as noted by Drake in his response, a large body of published data suggests that T cells responding to homeostatic proliferation are in fact more functional than their nonproliferating counterparts, and they acquire an effector phenotype during the process.²⁹ Thus based on thoughtful

evaluation of all the data, concerns about the efficacy of this vaccine should be allayed and this should have no impact on the clinical utility of sipuleucel-T.

PSA-TRICOM

An alternative approach to therapeutic cancer vaccines is demonstrated by PSA-TRICOM, a vector-based vaccine that consists of 2 poxviruses administered sequentially. This strategy is designed to generate an *in vivo* immune response, without the need for *ex vivo* cellular processing that is both costly and logistically cumbersome.^{7, 30} The poxviruses is used as a vehicle to transport targeting information to the immune system and thereby trigger an antitumor response. The large genome of the poxviruses makes them well suited for this role.³¹ In PSA-TRICOM, transgenes for PSA and 3 T-cell costimulatory molecules have been inserted into the genome. Vaccinia (used in rV-PSA-TRICOM) has a long track record of safety established by its use in the smallpox vaccine. The second virus used in this vaccine construct is fowlpox (rF-PSA-TRICOM), considered to be quite safe as it does not replicate in humans.⁷

Once the viruses have been injected subcutaneously, they can infect immune cells and antigen-presenting cells at a high rate.³¹ The genetic material inserted within the poxviruses is then translated, resulting in the immunologic expression of both PSA and the T-cell costimulatory molecules on the surface of antigen-presenting cells. Together they provide a powerful activating signal for CTLs, which then seek out and destroy cancer cells that express PSA.³²

Early clinical trials not only demonstrated the safety of this approach, with injection-site reactions and fevers the most common toxicities, but also confirmed the efficacy of a heterologous prime-and-boost strategy.^{33–37} Vaccinia initially generates a robust immune response, but neutralizing antibodies can negate the impact of subsequent doses of rV-PSA-TRICOM.³⁸ For this reason, all subsequent doses of vaccine are rF-PSA-TRICOM.³⁷

Based on the safety established in early trials, 2 phase II trials were conducted, both in mCRPC. One trial was conducted as a single-arm trial in 32 patients. The median overall survival in this trial was 26.6 months, which was similar to that seen in the sipuleucel-T trials. This study suggested that patients with more indolent disease characteristics benefited most from the vaccine. Furthermore, 13 of 29 evaluable patients had a > 2-fold increase in PSA-specific CTLs to a single 9-mer HLA-restricted peptide after treatment with vaccine. Although this cannot be considered a surrogate marker of response (indeed, patients without substantial changes in PSA-specific CTLs did well clinically), there was an association between magnitude of CTL response (6-fold increase) and improved survival.³⁹

In a second, multicenter trial of PSA-TRICOM (n = 125), patients were randomized 2:1 vaccine to placebo. This trial, also in patients with mCRPC, did not show a change in median TTP, similar to the sipuleucel-T trials. Ultimately, though, a significant improvement in overall survival was seen. Patients treated with vaccine survived a median of 25.1 months vs. 16.6 months for patients in the placebo arm (HR: 0.56, 95% CI, 0.37 to 0.85).⁴⁰

Based on these 2 studies, which suggested both the ability to generate a tumor-specific CTL response and a potential relative improvement in overall survival compared to placebo, a randomized, placebo-controlled phase III trial of PSA-TRICOM is ongoing. The study is enrolling patients with asymptomatic or minimally symptomatic mCRPC, with overall survival as the primary endpoint. Results of this trial are expected in 2016.⁴¹

Ipilimumab

Ipilimumab is an immune checkpoint inhibitor that binds to CTLA-4, a molecule expressed on CTLs after activation by antigen-presenting cells. This humanized antibody, administered via intravenous infusion, binds to CTLA-4 and prevents interactions with antigen-presenting cells that would otherwise quell CTL activity, leading to a more aggressive immune response.¹⁰ Ipilimumab is FDA-approved for the treatment of relapsed metastatic melanoma, but phase III trials are ongoing in both chemotherapy-naïve and chemotherapy-refractory mCRPC.⁴²

In early clinical trials, ipilimumab demonstrated a more complex toxicity profile than those seen with therapeutic cancer vaccines.¹³ This characteristic is likely due to the unfocused nature of the aggressive CTLs that ipilimumab generates. Commonly seen toxicities include dermatitis, colitis, panhypophysitis and thyroiditis. There has been some indication that these irAEs are associated with improved clinical outcomes, but that has not been universally demonstrated.^{43–44}

Ipilimumab was approved by the FDA for use in relapsed metastatic melanoma after demonstrating improved overall survival in a phase III trial⁴⁵ that randomized patients to treatment with GP100 (an older, peptide-based vaccine used as an active control), GP100 with ipilimumab, or ipilimumab alone. Similar to the sipuleucel-T and PSA-TRICOM trials previously discussed, there was no significant difference in TTP in the 3 arms, but there was an improvement in survival for patients in the 2 arms that received ipilimumab. The ipilimumab-alone arm showed improved median survival relative to GP100 alone (10.1 vs. 6.4 months, respectively; HR: 0.68; 95% CI, 8.0 to 13.8), while patients receiving ipilimumab with GP100 had a median survival of 10.0 months (HR: 0.66; CI, 8.5 to 11.5).

An early trial of ipilimumab in prostate cancer showed a toxicity profile similar to the same agent used against other tumor types; a minority of patients (2 of 12) had significant (> 50%) PSA responses.⁴⁶ A phase II study evaluated ipilimumab with radiation to isolated bone metastases in 29 chemotherapy-naïve and previously treated patients. Based on data suggesting that radiation can enhance the immune response, patients were treated with 800 cGy to 3 bone sites before starting ipilimumab. The rate of irAEs was similar to previously reported rates, and 5 of 29 patients had > 50% PSA declines.^{47–48}

Two phase III trials with ipilimumab are being conducted in patients with mCRPC. The first study in chemotherapy-naïve mCRPC is randomizing patients to ipilimumab as a single agent vs. placebo.⁴⁹ Another trial is combining limited radiation (similar to the phase II trial) with ipilimumab vs. limited radiation with placebo in the post-chemotherapy mCRPC setting.⁵⁰ These trials will ultimately define the role of immune-checkpoint inhibition in mCRPC and determine whether potential irAEs are offset by clinical benefits.

Anti-PD-1/Anti-PD-L1

Alternative immune checkpoint inhibition strategies are also in the early stages of clinical investigation. Programmed cell death protein 1 (PD-1) and its ligand (PD-L1) have been implicated as critical mediators of immune regulation, similar to CTLA-4.^{51–52} Early clinical trials have suggested antitumor activity with fewer irAEs than are seen with ipilimumab.^{53–55} If this clinical experience is maintained in current and future trials, immune checkpoint inhibitors could potentially play a greater role in prostate cancer, especially in the large proportion of patients with asymptomatic disease who may choose not to risk the irAEs typically experienced with ipilimumab.

HOW IMMUNOTHERAPIES DIFFER FROM OTHER CANCER THERAPIES

Indirectly targeting tumors through immune activation is just one of many differences between immune-based therapies and standard therapies. Therapeutic cancer vaccines also have minimal treatment-related toxicities, most commonly injection-site reactions or transient fever/flu-like symptoms. Immune-based therapies are particularly attractive in non-metastatic, recurrent prostate cancer. Elevated or rising PSA levels can indicate biochemical recurrence before there is any radiographic evidence on scans, making prostate cancer detectable in the micrometastatic state. This, plus the modest side-effect profile of vaccines, has given rise to many vaccine trials in nonmetastatic and newly diagnosed prostate cancer.^{25, 56}

Once an immune response is generated by a vaccine or immune checkpoint inhibitor, the activated immune response is potentially sustainable beyond the period of treatment.^{57–58} The immune response may also evolve over time, continuing to induce an antitumor response while also targeting new tumor antigens. Previous clinical trials have demonstrated that while vaccines may target a single tumor antigen such as PSA or PAP in prostate cancer, the ensuing immune response may actually be much broader. CTLs may target multiple tumor antigens not specified in the initial vaccine construct and not present prior to vaccine therapy, likely the result of a phenomenon known as antigen spreading or antigen cascade. As activated immune cells, and even subsequent therapies, lyse tumor cells, additional tumor antigens are released into the tumor microenvironment. An activated immune milieu can process these new antigens and present them to CTLs as new potential targets,⁵⁹ as has been demonstrated in several vaccine trials in prostate cancer and other tumor types.^{56, 60–62} In this manner, immune responses may be sustained over the long term, even as the tumor mutates to present a different prevalence of antigen expression.

Antigen cascade has significant implications for the optimal use of immune-based therapies. If relatively nontoxic vaccine therapies can have a sustained impact over the long term, their potential for clinical benefit will be greatest if they are administered in the early stages of disease.⁶³ However, this strategy has potential limitations. Most notably, the phase III trials of sipuleucel-T and ipilimumab (in metastatic melanoma) and the randomized phase II trial of PSA-TRICOM demonstrated no short-term evidence or intermediate marker of clinical benefit.^{22, 40, 45} Large decreases in tumor volume are unlikely to be seen with immune-based strategies in the majority of patients, especially in the short term. Without changes in tumor volume or PSA (which was relegated to a secondary marker of response by the Prostate Cancer Clinical Trials Working Group Guidelines in 2008), practitioners and patients face a perplexing dilemma: How can one know if the therapy is working?⁶⁴ And perhaps more importantly, how can one know when to move on to the next course of therapy? Although modified immune-related response criteria have been developed to better differentiate disease progression and objective response with immune-based therapies, there are currently no clear biomarkers of response.⁶⁵

Determining Response

Although it is well understood that immunotherapies are fundamentally different from standard cytoreductive therapies, the expectations for immunotherapy do not reflect this discrepancy. Patients and practitioners have an urgent need for a marker to determine short-term benefit, a marker that has been elusive in immunotherapy trials that have nonetheless demonstrated improvement in overall survival. A rational expectation would be to identify an immune (bio)marker of activation that could be evaluated in a patient's blood weeks or months after initiation of treatment to confirm benefit. Such a surrogate might quell the concerns of a patient with rising PSA, for example. Unfortunately, no such biomarker has been identified as yet. CD54 expression on immune cells has been incorporated into the

release criteria for sipuleucel-T as a possible marker of immune activation, and an association between CD54 expression and clinical response has been suggested.¹⁷ In addition, CTL responses have been associated with improved clinical outcomes with PSA-TRICOM, but the absence of these findings do not necessarily preclude the possibility of benefit. In these important aspects, such immune parameters fail as true surrogates.³⁹

Although many ongoing clinical trials and retrospective analyses of clinical trials are evaluating biomarkers of immune response, it appears that this reasonable expectation could remain elusive for some time to come, probably because of the complexity of the immune system and the variable mechanisms of effective immune response that may be at work in different patients with the same form of immune stimulation. The phenomenon of antigen spreading or antigen cascade observed in multiple trials^{56, 60–62} clearly demonstrates the variability and complexity of the immune response. Patients treated with certain immune-stimulating therapies that target specific tumor antigens, such as PSA or PAP, have been observed to have robust immune responses to secondary antigens. Ultimately, the immune response may target these secondary antigens with even greater vigor than the initiating antigen targeted in the immune-stimulating therapy. Thus, if an immune biomarker were designed to evaluate CTL response to the therapy's primary targeted tumor antigen, the absence of a significant CTL response to that particular antigen would not necessarily preclude a significant immune response to a secondary antigen as part of an antigen cascade. Although panels to multiple antigens of CTL response can be done, it may be difficult to know which is most relevant in a given patient's tumor. Furthermore, this broadening of the CTL response only represents one component of the immune system. It is quite possible that other aspects of the immune system could respond similarly, supplanting the CTL response as the major impetus of the immune system's antitumor response. Such immune components as natural killer cells, B cell-mediated antibody responses, tumor-associated macrophages, and down-regulation of previously amplified immune-regulatory mechanisms could all play a significant role in an immune-mediated antitumor response, yet vary greatly from patient to patient.^{61, 66–67}

Alternative Strategies to Assess Response to Immunotherapy

The lack of intermediate markers of response is a very real impediment to the appropriate deployment of immune therapies in prostate cancer.⁶⁸ One emerging strategy is based on data that suggest that immune-based therapies may alter tumor growth rate over the long term, resulting in short-term disease progression that belies the underlying modulation of tumor growth. A recent analysis of 5 prostate cancer studies conducted at the National Cancer Institute (NCI), including one using the vaccine PSA-TRICOM, evaluated the impact of the various treatments on tumor growth rates.⁶⁹ Tumor growth rates are based on tumor growth and regression kinetics and have been modeled using several relevant disease parameters, including tumor measurements in renal cell cancer, M-spikes in multiple myeloma, and PSA in prostate cancer.^{70–71} A mathematical equation that calculates tumor growth rates based on these parameters can be used to estimate survival times with reasonable accuracy.

When the 4 NCI trials that used chemotherapy were evaluated, the results were consistent with other cytoreductive therapies in other tumor types. Chemotherapy-based treatment temporarily altered or decreased the growth rate while patients were on the therapy, but once the therapy became less effective or was discontinued, the growth rate reverted to pretreatment rates and death was predictable based on the mathematical equation and off-study growth kinetics.⁶⁹ The vaccine trial involving PSA-TRICOM, however, was not consistent with this previously demonstrated model. In this trial, no change in tumor growth rate was seen while patients were on-study, consistent with the trial that had a median disease progression by conventional measures at 3 months.³⁹ However, unlike patients on

chemotherapy, these patients' mortality could not be predicted by their post-treatment, off-study growth rates. Instead, these patients' survival times were markedly more prolonged than would have been anticipated by their off-study growth rates. A separate analysis of this population indicated that subsequent therapies did not differentially improve survival for patients with better vs. poor outcomes, suggesting that benefit from ensuing treatment does not account for this apparent disconnect between off-study growth rate and a far better survival time than would have been predicted using this model.^{39, 69}

One hypothesis regarding this outcome appears to be supported by data from other trials. Perhaps the tumor growth rate, which was not significantly altered in the median 3 months on treatment, was altered in the months post-treatment to such a degree that it improved survival.⁷² (Table 2) While this would be an unrealistic outcome with chemotherapy or hormonal therapy, given their transient impact, it is plausible with immune therapies, which can initiate a persistent immune response that may evolve through antigen spreading well beyond the treatment period. Ongoing trials, including the phase III study of PSA-TRICOM in mCRPC,⁴¹ will prospectively evaluate whether a dynamic immune response initiated by vaccine can gradually reduce tumor growth rate enough to substantially improve survival. As opposed to trials with cytoreductive that may decrease PSA or tumor volume transiently, immunotherapy gradually may slow PSA/tumor growth rate over time, perhaps resulting in a near-term rise in PSA/tumor volume but a generally slower pace of disease over the long term, relative to controls.

Previous clinical trial experience may support the hypothesis that modern immune therapies alter tumor growth rate without altering short-term disease progression, as evaluated by conventional measures such as PSA or RECIST-based imaging assessments. Indeed, multiple phase III trials of sipuleucel-T in mCRPC, a phase III trial of ipilimumab in melanoma, and the phase II trial of PSA-TRICOM in mCRPC all reported improved survival without changes in short-term disease progression.^{22, 40, 45} These findings are consistent with the phenomenon of altered tumor growth kinetics following immune-based treatment, which affect long-term survival in the absence of any short-term decrease in tumor burden.

Two other trials in nonmetastatic castration-sensitive prostate cancer (nmCSPC) have suggested that vaccines have the ability to alter tumor growth rate, as measured by PSA doubling time (PSA DT). ECOG 9802 treated men with nmCSPC with PSA-TRICOM monthly for 3 months and then once every 3 months. In a preliminary analysis of 29 patients who had been on-study for more than 6 months, a significant decrease in PSA DT was noted, from 4.4 months at enrollment to 7.7 months ($P = 0.002$), again providing evidence that PSA-TRICOM may modulate tumor growth after administration.⁷³ Since there is no control in this post-hoc analysis, caution should be used in over-interpreting such findings, although similar results were seen in a second randomized trial.

A second trial in nmCSPC randomized patients 2:1 to receive sipuleucel-T ($n = 117$) or placebo ($n = 59$) after 3 to 4 months of androgen-deprivation therapy (ADT).²⁴ Although there was no significant change in biochemical failure (a measure of TTP in this patient population), there was a significant change in PSA DT after testosterone recovery. For patients who received sipuleucel-T, PSA DT after testosterone recovery was 155 days compared to 105 days for the placebo group ($P = 0.038$), again suggesting the impact of vaccine and its ability to modulate tumor growth.

Ultimately, trials with prospective endpoints that evaluate growth rates, such as the PSA-TRICOM phase III study in mCRPC, will have to provide stronger evidence that vaccine can alter growth rate, and then demonstrate that such changes are associated with improved

clinical outcomes such as survival. If this can be established, the growth rate equation previously described may allow practitioners to evaluate patients within a few months of initiating an immune-based therapy. Data evaluating tumor growth rate while on an immune-based therapy may provide an intermediate signal of the moderating effects of these treatments on the growth of prostate cancer.

FUTURE DIRECTIONS

Combination Therapy

Although analysis of tumor growth rates may help to clarify the benefits of immunotherapy as a monotherapy for prostate cancer, the true potential of immunotherapy may be in combination with standard approaches such as radiation and ADT. (Table 3) Furthermore, if immunotherapy can have long-term, sustained effects on prostate cancer (including growth rate), even after treatment has been completed, the rational approach would be to use it early in the disease process rather than when patients have metastatic disease and a predicted survival of 2 to 3 years. Decreasing the growth rate in patients with nonmetastatic disease may result in a greater impact on survival than that reported in previous trials.

There is strong evidence that radiation therapy, one of the cornerstones of definitive treatment in prostate cancer, can enhance the immune response. Even at nonlethal doses, such as those given at the center of a tumor mass where radiation may have its least cytotoxic impact,⁴⁷ radiation therapy has been shown to stress tumor cells, leading to up-regulation of key genes that alter phenotypic expression of tumor cells in an immunologically relevant manner.⁷⁴ Enhanced expression of major histocompatibility complex molecules, ICAM-1, and Fas, in addition to TAAs, has been shown to enhance T cell-mediated tumor killing.⁷⁵ In addition, radiation can enhance chemokine production by tumor cells, resulting in enhanced immune-cell trafficking to the tumor.⁷⁶

Data from one clinical trial corroborate evidence indicating that immunotherapies can capitalize on the immunogenic modulation effects of radiation therapy. Thirty patients with untreated prostate cancer were randomized to either standard radiation (n = 11) or standard radiation plus a poxviral vaccine targeting PSA.⁵⁶ The combination of radiation with vaccine was well tolerated and did not result in increased toxicities. The immunologic results of the study indicated that 13 of the patients who received vaccine with radiation had a 3-fold increase in PSA-specific immune cells, compared to patients who received radiation alone. Furthermore, several patients treated with vaccine and radiation had T-cell responses to tumor antigens induced by antigen cascade, as well as evidence of antibody responses, both of which speak to the potential for synergy between radiation and vaccine.^{56, 61}

The potential immunogenic modulation effects of radiation are being incorporated in an ongoing phase III trial of ipilimumab in mCRPC. Patients previously treated with docetaxel are being given radiation to isolated bone metastases, followed by ipilimumab or placebo. There is not a control group receiving no radiation and ipilimumab.

Promising but anecdotal abscopal effects have also been seen in a melanoma patient treated with ipilimumab and radiation, where tumor well beyond the radiation field significantly decreased in size.⁷⁷ Abscopal effects are yet to be reported in prostate cancer. Although promising, the toxicity of ipilimumab with definitive radiation in newly diagnosed prostate cancer patients is likely too high to be evaluated, given the potential for long-term sequelae of irAEs in patients who could be cured with radiation alone.

Another standard component of prostate cancer therapy is ADT, an approach also associated with potential immune enhancement.⁷⁸ Previous studies have shown that ADT can enhance T-cell trafficking to the prostate within weeks after administration.⁷⁹ Furthermore, ADT has been shown to enhance naïve T-cell production from the thymus, a population that could be activated by an immune therapy and directed at prostate cancer cells and antigens.⁸⁰ Other data suggest that ADT can decrease self-tolerance of immune cells, making them more likely to attack cancer cells that overexpress self-antigens.⁸¹

Given these potential immune-augmenting qualities, it would be rational to combine nontoxic therapeutic cancer vaccines with ADT in patients early in the disease process, such as in nmCSPC (as in the previously described combination of sipuleucel-T and ADT).²⁴ In addition, early promising data are emerging from an ongoing trial evaluating an androgen receptor antagonist (flutamide) with PSA-TRICOM in nonmetastatic CRPC.⁸² Enzalutamide, a well tolerated and more effective androgen receptor antagonist, will likely be used early in the disease process. Evidence of the long-term impact of enzalutamide with a vaccine in nonmetastatic prostate cancer is eagerly anticipated.⁸³

Both radiation and ADT have an important role in treating patients with newly diagnosed, high-risk prostate cancer. An ongoing, randomized study of vaccine in combination with these modalities is underway in this patient population to evaluate immunologic impacts.⁸⁴ If the data are promising, it would be reasonable to investigate whether such a combination could enhance clinical outcomes for patients with high-risk disease. Given the potential long-term moderating effects on immune stimulation and growth moderation, as well as minimal toxicities, starting vaccines at the time of definitive therapy appears to be a rational approach. In addition to combination radiation trials, pilot studies of sipuleucel-T prior to radical prostatectomy have also been conducted which demonstrate an increased immune infiltrate in vaccinated patients.²⁵ In this study 42 patients received sipuleucel-T at 3 two-week intervals prior to radical prostatectomy. Interestingly, there was a significant increase in CD3+ and CD4+ T-cells at the interface of normal prostate tissue and malignant prostate tissue, compared to pre-treatment biopsies and benign prostate tissue removed at surgery. These data suggest that sipuleucel-T may be able to induce lymphocyte infiltration of tumor, but additional studies are required to determine the clinical significance.

There is an increasing rationale for combining multiple immunotherapies, with the goal of generating a greater immune response that results in enhanced antitumor activity. Preclinical data suggest that different vaccine modalities work through different mechanisms, augmenting disparate populations of immune cells.⁸⁵ Two different vaccines have been combined with ipilimumab in mCRPC. The combinations did not appear to significantly enhance toxicity, but there was a suggestion of enhanced clinical outcomes.^{44, 86} Future randomized trials will be required to confirm and expand these preliminary findings.

IMMUNOTHERAPY COMBINATIONS MAY IMPACT SHORT-TERM PROGRESSION

Perhaps the most important implication of combining immunotherapy with cytoreductive therapies is that it may result in improved short-term TTP, potentially achieving 2 goals, first, obviating the need to identify elusive intermediate biomarkers of response. The change in short-term TTP (i.e. 3 months as seen with more conventional cytoreductive therapies) may occur with combinations but not with immune monotherapy because of the combined effects of the treatments. Thus, cytoreductive therapies (radiation, ADT, or chemotherapy) will allow time for immune therapies to potentially generate a meaningful immune response. If immune therapies can alter tumor growth rate, as previously suggested, then as tumor begins to regrow after maximal response to the partner cytoreductive agent, it will do so at a

slower rate, thereby prolonging disease progression.^{69, 72} Second, by combining, immunotherapies as we now know them will be easier to administer and will gain wider acceptance since intermediate endpoints such as PSA decline and objective changes will not be as heavily relied on by patients and physicians to monitor benefit.

Preliminary data from multiple clinical trials support the hypothesis that immunotherapy with cytoreductive therapy can prolong TTP relative to cytoreductive therapy alone. In a study of metastatic breast cancer patients, docetaxel combined with a poxviral vaccine targeting MUC-1 and CEA prolonged TTP 6.6 months vs. 3.8 months ($P = 0.12$; HR = 0.67, 95% CI: 0.34 to 1.31).⁸⁷ Preliminary trials in prostate cancer also separately suggest that the antiandrogen flutamide and the radioisotope samarium-153 can have enhanced effects on TTP when combined with PSA-TRICOM, compared to the respective treatments alone.^{82, 88} It is also important to note that in all 3 of these trials, the vaccine did not enhance the toxicity of the cytoreductive agent.

Although more robust, randomized clinical trials with modern agents (such as enzalutamide or radium-223 in prostate cancer) are required, the impact of combination therapy on TTP is potentially vital to the future role of immunotherapy in prostate cancer. If these immune treatments can in fact be combined with cytoreductive therapies and thus improve TTP, the greatest impediment to their clinical use—lack of intermediate markers of response—will have been removed. Ultimately, successful immunotherapy could be deployed as an adjuvant of sorts for immune-enhancing cytoreductive therapy such as ADT or radiation. This could improve clinic outcomes in both the short term (TTP) and long term (overall survival) by generating sustained immune-mediated antitumor responses. Moreover this will allow for wider adoption of immunotherapies given that a lack of short-term indicators which suggest improved TTP (and thus indication of clinical benefit) has likely played a significant role in limiting the utilization of sipuleucel-T.

CONCLUSION

Modern immunotherapies may further change the landscape of evolving therapies in prostate cancer. Both immune checkpoint inhibitors and therapeutic cancer vaccines have demonstrated merit in early trials, while sipuleucel-T has taken its rightful place among viable treatment options for men with minimally symptomatic mCRPC. Ongoing trials of PSA-TRICOM and ipilimumab may increase the immunotherapy options available to patients with mCRPC. The potential for immunotherapies to exert sustained immune effects beyond their period of administration, along with the possible immune-enhancing impact of ADT and radiation therapy, has led to increasing numbers of immunotherapy combination trials, many in early-stage disease. If combination trials ultimately confirm the ability of immunotherapy to enhance TTP in combination with cytoreductive therapies, then the need for intermediate biomarkers of immune response may be obviated and the confusion surrounding immunotherapy and its clinical effects may resolve. The ultimate role of immunotherapy may be as an agent that enhances other therapies in the short term, improves survival in the long term, and does not burden patients with additional toxicities.

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Table 1**Leading Immunotherapy Strategies in Prostate Cancer**

Therapeutic Cancer Vaccines. Designed to stimulate immune cells that ultimately target tumor antigens and destroy cancer cells, without significant toxicity.	
<ul style="list-style-type: none"> • <i>Ex Vivo</i> Processed Vaccines: Require cellular processing that can be costly but may lead to optimal immune activation. Currently the only FDA-approved strategy in mCRPC (sipuleucel-T).²² • Vector-Based Vaccines: An off-the-shelf approach that delivers an immune stimulatory message <i>in vivo</i> to immune cells. One such vaccine, PSA-TRICOM, is currently in phase III testing in mCRPC.⁴⁰ • Whole Tumor-Cell Vaccines: Irradiated tumor cells are injected into the patient to provide multiple targets for the immune system. After failure in previous phase III trials (GVAX for prostate cancer), further studies are required to better understand and optimize this approach.⁸ 	
Immune Checkpoint Inhibitors. Interfere with the immune system's autoregulatory mechanisms, thereby enhancing T-cell activity and potentiating antitumor effects.	
<ul style="list-style-type: none"> • Anti-CTLA-4: The leading agent in this category is ipilimumab, FDA-approved for the treatment of metastatic melanoma and currently in phase III testing in mCRPC (pre- and post-chemotherapy with limited radiation). Immune-related adverse events are common and likely prevent this strategy from moving into nonmetastatic prostate cancer.^{45, 49-50} • Anti-PD-1/PDL-1: An emerging alternative to anti-CTLA-4 with a purportedly less toxic side effect profile; still in early stages of clinical testing.⁵⁴⁻⁵⁵ 	

Table 2**Immunotherapy May Modulate Tumor Growth Rates Over Time**

Hypothesis: Consistent with their potential to induce long-term and sustained immune responses, immunotherapy over time induces an immune response that rarely diminishes tumor burden, but decreases tumor growth rates. Although potentially considered progression in the short term, tumor growth rate could slow over time and thus substantially improve long-term outcomes such as survival.	
Many Modern Immunotherapy Agents Improve Survival, But Do Not Suggest Changes in Short Term Time to Progression	
<ul style="list-style-type: none"> Sipuleucel-T: Improved overall survival in 2 phase III trials but did not alter time to progression in mCRPC.²² Ipilimumab: Improved overall survival in a phase III trial in metastatic melanoma, but did not alter time to progression.⁴⁵ PSA-TRICOM: A phase II study in mCRPC demonstrated no change in time to progression, but improved overall survival.⁴⁰ 	
A Retrospective Analysis of NCI Clinical Trials Suggests that Vaccine Moderates Tumor Growth Rate Over Time	
<ul style="list-style-type: none"> Patients treated with cytotoxic therapy had predictable survival times based on off-study tumor growth rates.^{69–70} Patients treated with vaccine (PSA-TRICOM) had unaltered tumor growth rates relative to enrollment, but survival went well beyond that predicted by growth rate, suggesting a moderation of tumor growth rate occurred over time after therapy was initiated.⁶⁹ 	
PSA-TRICOM Prolonged PSA Doubling Time in 6 Months in Nonmetastatic Patients with Normal Testosterone	
<ul style="list-style-type: none"> Patients with nonmetastatic castration-sensitive prostate cancer and normal testosterone treated with PSA-TRICOM vaccine monotherapy had an improvement in PSA doubling time of 4.4 to 7.7 months after 6 months in a post-hoc analysis ($P = 0.002$).⁷³ 	
Sipuleucel-T Improved PSA Doubling Time after Testosterone Normalization	
<ul style="list-style-type: none"> Patients with nonmetastatic castration-sensitive prostate cancer and normal testosterone were treated with 3 to 4 months of ADT and then sipuleucel-T or placebo. Patients who received sipuleucel-T had a 48% longer PSA doubling time after testosterone normalization (155 vs. 105 days; $P = 0.038$).²⁴ 	

Table 3

Future Immunotherapy Strategies in Prostate Cancer

Start Immunotherapy Earlier in the Disease Process	
<ul style="list-style-type: none">If immunotherapy alters tumor growth rate, starting such therapies earlier in the disease process could enhance clinical outcomes over the long term.⁷²	
Combine Immunotherapy with Radiation or ADT	
<ul style="list-style-type: none">ADT can enhance T-cell trafficking, mitigate immune tolerance, and increase thymic production of naïve T cells.^{79–81}Radiation therapy can enhance antigen expression and immune-mediated tumor cell killing.^{74–75}	