Therapeutic Vaccines and Immunotherapy in Castration-Resistant Prostate Cancer: Current Progress and Clinical Applications

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Overview

Results of recent clinical trials have intensified interest in immunotherapy for cancer. Among the most promising candidates for immunotherapy are patients with prostate cancer. Results of therapeutic vaccine clinical trials in this population have suggested statistically significant and clinically meaningful improvements in overall survival, with substantially fewer side effects than with chemotherapy. Of particular interest are sipuleucel-T, the first U.S. Food and Drug Administration-approved therapeutic cancer vaccine, and PSA-TRICOM (PROSTVAC), a therapeutic cancer vaccine in phase III testing. The immune checkpoint inhibitor ipilimumab is also stirring considerable interest, with two phase III trials ongoing in prostate cancer. This article highlights data emerging from these trials and addresses remaining questions and practical clinical implications of this therapeutic strategy.

The goal of immunotherapy for cancer is to induce the immune system to attack tumor tissue. Strategies for generating a therapeutic immune response include the use of therapeutic vaccines designed to target specific tumor epitopes, and immune checkpoint inhibitors that allow for the expansion of an underlying immune response and that may also target regulatory T cells at the site of the tumor. Prostate cancer is particularly amenable to immunotherapy for a variety of reasons.¹ First, because the prostate is a nonessential organ, eradication of residual normal prostate tissue by an immune response results in no clinical sequelae to patients. More importantly, many well-defined prostate-associated antigens are known to be immunogenic. One of these, prostate-specific antigen (PSA), can also serve as an excellent marker of disease progression. Finally, because prostate cancer is relatively indolent, potentially immune suppressive chemotherapy is generally not used until later in the disease course.

SIPULEUCEL-T

Sipuleucel-T (Provenge, Dendreon Corporation) was recently approved by the U.S. Food and Drug Administration for use in patients with mCRPC. Sipuleucel-T is a unique vaccine

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platform that requires leukapheresis of patient blood samples. At a central processing laboratory, antigen-presenting cells obtained from patient samples are enriched and incubated with a fusion protein consisting of prostatic acid phosphatase linked to the immunomodulatory cytokine granulocyte-macrophage colony-stimulating factor. The vaccine is then returned to the patient's health care provider for infusion. This procedure is performed three times over approximately 1 month. Results from a randomized phase III trial of sipuleucel-T demonstrated a median overall survival of 25.8 months compared with 21.7 months for the placebo (4.1 month; Fig. 1A).² Interestingly, although the primary end point of survival was clearly attained ($p = 0.032$), there was no statistical difference in time to progression (TTP) compared with the results from the placebo. These results were almost identical with a previous phase III trial with sipuleucel-T, in which the primary end point was TTP.³ Both studies showed no improvement in TTP, but demonstrated a clear statistical improvement in median overall survival compared with the placebo. Data from the later phase III study also suggest that patients with more potent immune responses following vaccine have improved overall survival.⁴

PSA-TRICOM

PSA-TRICOM (PROSTVAC) is another cancer vaccine that has been evaluated in metastatic castration-resistant prostate cancer (mCRPC). This off-the-shelf, vector-based vaccine consists of a prime-boost regimen (recombinant vaccinia prime and five to six recombinant fowlpox boosts). Each of the recombinant poxviruses contains transgenes for PSA and three co-stimulatory molecules (TRICOM) designed to boost the immune system. A multicenter randomized phase II trial in mCRPC demonstrated that patients who received PROSTVAC had improved overall survival. At three years poststudy, 30% of vaccinated patients were alive compared with 17% of the controls. The median overall survival was 8.5 months. The survival rate was longer for vaccinated patients than for the controls (25.1 vs. 16.6 months, $p = 0.0061$, hazard ratio: 0.56; Fig. 1B).⁵ Notably, as in the two sipuleucel-T trials, there was no difference between the two arms in terms of TTP, and toxicity was minimal. Another study suggested that patients who mount the most vigorous immune response to vaccine may have improved survival.⁶ A subsequent analysis of samples from these two studies suggested that a pre-existing antibody to a glycoprotein antigen in the vector was also associated with improved outcome in patients treated with vaccine, but not the wild-type vector.⁷

IPILIMUMAB

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a human immunoglobulin G-1 kappa monoclonal antibody that targets cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Ipilimumab was the first in a class of therapies targeting T-cell activation and regulation to be licensed in the broad category of agents known as immune checkpoint inhibitors, based on improved overall survival in patients with metastatic melanoma.⁸ Interestingly, the melanoma study demonstrated a lack of improvement in median TTP similar to that seen in prostate studies, suggesting that this kinetic profile may be characteristic of immunotherapies as a class. A unique set of toxicities referred to as immune-related adverse events has been seen with the use of anti-CTLA-4 antibodies, including infiltration of

inflammatory cells into nonsterile epithelial surfaces (i.e., colon and skin, which likely have ongoing immune activity) and endocrine organs (i.e., thyroid, adrenals, and pituitary, which have been associated with autoimmune disease). In most instances, these immune-related adverse events can be readily managed medically.

Early studies of ipilimumab in prostate cancer have led to two phase III clinical trials, one in chemotherapy-naïve patients with mCRPC and a second in combination with radiation in patients with mCRPC previously treated with chemotherapy. Results from the latter trial are expected in spring 2013. In addition, two phase I dose-escalation trials of ipilimumab in combination with therapeutic vaccines in patients with mCRPC have demonstrated encouraging activity.^{9,10} Finally, other immune checkpoint inhibitors such as anti-PD1 or anti-PDL1 may find utility in prostate cancer either as single agents or in combination with therapeutic vaccines or other strategies.

PARADOX

The clinical trials of sipuleucel-T and PROSTVAC demonstrated a significant and clinically meaningful improvement in overall survival in patients with mCRPC, with no associated improvement in TTP, which may be a class effect of immunotherapies. In the context of traditional cytotoxic therapies, this may seem counterintuitive. However, it must be understood that therapeutic cancer vaccines differ from conventional therapies in several distinct ways (Table 1). First, their primary target is not the tumor itself, but the immune system, which subsequently targets the tumor. It may take weeks to months to mount a clinically significant immune response following vaccination.¹¹ However, vaccines may induce the development of long-lived memory cells with the potential to provide continuous immunologic pressure that results in a slowing of the tumor's net growth rate. Within a tumor, new cells are constantly being produced while other cells are dying. The rate of tumor growth is thus influenced by tumor biology (the intrinsic rate at which new daughter cells are formed) offset by host biology (the rate of tumor-cell loss resulting from antitumor immune response), combined with factors introduced into the tumor environment (e.g., killing of tumor cells by conventional therapies).

An effective anticancer immune response may reset the tumor-growth equilibrium so that more tumor cells are killed by the immune system. This effect may not translate into objective responses or short-term improvements (within 3 to 4 months) in TTP, but because this effect may be both long-lasting and augmented by subsequent therapies,^{12,13} the end result may be eventual slowing of the tumor growth rate, leading to improved overall survival (Fig. 2).¹⁴ Indeed, recently published data from prostate cancer vaccine trials at the National Cancer Institute support the concept of eventual decreased tumor growth rate following treatment with a therapeutic vaccine.¹⁵ Furthermore, unlike traditional therapies, an ongoing, dynamic immune response can adapt to subsequent mutations within the tumor, continuing or expanding a therapeutic response.

This new understanding of the kinetics of clinical response following treatment with a therapeutic vaccine, coupled with clinical experience showing that an end point of overall survival may be the only valid discriminator of activity in single-agent vaccine studies, poses

a dilemma for accelerating proof-of-concept studies. Because trials with a survival end point typically take years to accrue and mature, identifying and validating intermediate end points is crucial to facilitating efficient life cycles for phase II studies in immunotherapy for prostate cancer.

IMMUNE END POINTS AND ANTIGEN CASCADE

It has been suggested that a broader immune response caused by expansion of a T-cell response to epitopes not found in the vaccine may lead to a more clinically relevant antitumor immune response.¹⁶ This concept, known as epitope spreading, antigen spreading, or antigen cascade, has been associated with both major histocompatibility complex class I- and II-restricted responses and reflects cross-presentation of tumor antigens. Thus, when tumor-specific T cells lyse tumor cells, the dead or dying tumor cells may be taken up by antigen-presenting cells, with the result that multiple, perhaps even more immunogenic, tumor antigens can be presented to immune cells, initiating a broader immune response.

As a consequence of antigen cascade, it is possible that the same vaccine may induce completely different immune responses in different patients with the same type of cancer. Furthermore, the immune response to antigens not present in the vaccine may continue over time, eventually broadening into an immune response that could be even more clinically relevant than the initial response to the epitope in the vaccine. Many examples of T-cell antigen cascade have been reported in clinical trials of therapeutic vaccines in patients with cancer,^{9,17–21} and several of these trials have suggested improved clinical outcomes for patients who demonstrated a broadened immune response.^{19–21}

Clearly, additional markers of efficacy would speed proof-of-concept studies; significant efforts are underway to meet this need. Emerging data suggest that TTP may be a meaningful discriminator of efficacy when immunotherapy is combined with standard-of-care therapies, compared with those therapies alone.²²

CLINICAL APPLICATION

The available data suggest that in patients with rapidly progressive or significantly symptomatic disease, vaccines will likely not be very effective and should not be used as a monotherapy. Indeed, the greatest clinical benefit is seen in patients with earlier-stage or less aggressive disease.^{6,23,24} After initiating a therapeutic vaccine, most patients will not experience a rapid, sustained decrease in PSA. Although this has been observed, it is typically seen in less than 5% of patients. Thus, effective treatment with immunotherapy, when given alone, requires careful selection of patients who are not likely to progress clinically within 3 to 6 months. In 20% to 30% of patients, treatment with ipilimumab may result in PSA decreases of at least 50%. Data from phase III clinical studies should soon confirm whether ipilimumab can improve overall survival in mCRPC.

The widespread use of glucocorticoids in therapeutic regimens for prostate cancer raises questions about the influence of these compounds on the immune response. It is quite possible that the ability to maintain, or even mount, an immune response in the face of daily glucocorticoids is not as problematic as one would expect, given that memory cells are

relatively resistant to steroid-induced killing compared with naïve cells.^{1,25} A clinical trial of sipuleucel-T with abiraterone and prednisone demonstrated that sipuleucel-T can be manufactured during treatment with abiraterone and prednisone with product potency and prime boost similar to that of sipuleucel-T alone.²⁶

Immune-oncology combinations have already demonstrated the potential for synergistic responses.^{12,13,27–29} Eventually, combining immunotherapies with other effective therapeutic strategies in prostate cancer may lead to improved disease control, delayed symptoms, and greatly improved survival. However, the path to this eagerly anticipated outcome must be paved with carefully designed, controlled clinical trials.

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FIG 1.

Overall survival curves for (A) sipuleucel-T (n = 516), and (B) PSA-TRICOM (n = 125).

(A) Reproduced with permission, New England Journal of Medicine, © 2010 Massachusetts Medical Society.² (B) Adapted from Journal of Clinical Oncology © 2010 American Society of Clinical Oncology.⁵

Abbreviations: PSA, prostate-specific antigen; TRICOM, triad of costimulatory molecules.

FIG 2.

Tumor growth is a dynamic biologic process that is the combined result of cells dividing and other cells dying. Intrinsic tumor biology, as well as extrinsic factors such as therapies, affect the tumor's growth rate. However, chemotherapy (red line) only affects the tumor growth rate while it is being administered, which may result in a dramatic but transient response. Following discontinuation of chemotherapy, the growth rate returns to its pretreatment slope, driven by the underlying biology of the tumor. Immunotherapy (blue line), on the other hand, can alter the biology of the host by inducing an active antitumor immune response including a memory response. This may not cause an immediate or dramatic change in tumor burden, but continued cumulative slowing pressure on tumor growth rate, especially if started early in the disease course, may lead to substantially longer overall survival. The arrow indicates the initiation of treatment; cross indicates time of death as a result of cancer. Adapted from Madan, *The Oncologist*, © 2010 AlphaMed Press.¹⁴

TABLE 1.

Comparisons between Conventional Therapies and Therapeutic Vaccines

CONVENTIONAL THERAPIES		
THERAPEUTIC VACCINES		
Target	Tumor/tumor Microenvironment	Immune system
Pharmacodynamics	Action often Immediate	Delayed action
Memory Response	No	Yes
Tumor Evolution/New Mutations	Create resistance to therapy	Create new immunogenic targets
Limitations	Toxicity	Require adequate immune function systemically and at tumor site