Immunotherapy for Prostate Cancer: Recent Advances, Lessons Learned, and Areas for Further Research

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Abstract

A surge of interest in therapeutic cancer vaccines has arisen in the wake of recent clinical trials suggesting that such vaccines can result in statistically significant and clinically meaningful improvements in overall survival—with substantially limited side effects compared with chemotherapy—in patients with metastatic castration-resistant prostate cancer. One of these trials led to the registration of sipuleucel-T, the first therapeutic vaccine to be approved for cancer patients. In this review we highlight emerging patterns from clinical trials that suggest a need for more-appropriate patient populations (i.e., with lower tumor volume and less-aggressive disease) and endpoints (i.e., overall survival) for studies of immunotherapy alone, as well as biologically plausible explanations for these findings. We also explore the rationale for ongoing and planned studies combining therapeutic vaccines with other modalities. Finally, we attempt to put these findings into a practical clinical context and suggest fertile areas for future study. Although our discussion focuses on prostate cancer, the concepts we address most likely have broad applicability to immunotherapy for other cancers as well. \textit{Clin Cancer Res; 17(12); 3884–91. ©2011 AACR.}

Introduction

Until recently, chemotherapy was the only treatment that had been shown to improve overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC). However, in the last decade, a better understanding of the immune system, combined with innovative treatment approaches, has led to promising improvements in OS, as well as approval by the Food and Drug Administration (FDA) of the first therapeutic anticancer vaccine, sipuleucel-T (Provenge; Dendreon Corp.). Sipuleucel-T is an autologous cellular product in which antigen-presenting cells, obtained by leukapheresis, are enriched and pulsed with a granulocyte macrophage colony-stimulating factor (GM-CSF)/prostatic acid phosphatase (PAP) fusion protein (Fig. 1)\textsuperscript{(1–3)}. This product is then administered 3 times over a period of 1 month. Early studies with sipuleucel-T showed no statistically significant improvements in time to progression (primary endpoint); however, improvements were seen in OS (1, 2). On the basis of improvements in OS seen in a 512-patient randomized, double-blinded, controlled, phase III IMPACT trial (25.8 versus 21.7 months, hazard ratio [HR] = 0.775, \(P = 0.032\)), the FDA approved sipuleucel-T for use in men with asymptomatic or minimally symptomatic mCRPC\textsuperscript{(4)}. It remains unclear why this approach succeeded where other cancer vaccines, in several disease settings, had previously failed. One factor that may have contributed to the success of the IMPACT trial is that trials of sipuleucel-T have generally enrolled asymptomatic or minimally symptomatic patients, an earlier-stage patient population that may be more amenable to immunotherapy, as discussed below. Another important factor may be that the control arm was treated with a placebo vaccine, in contrast to the VITAL-1 trial of the GVAX vaccine, in which the comparator arm was treated with standard chemotherapy. A placebo-controlled trial design for this patient population is reasonable, because there are no data suggesting that earlier use of chemotherapy is more effective. It is also possible that the difference in median predicted survival (by a validated nomogram\textsuperscript{(5)}) of 16 months for VITAL-1 versus 21 months for the IMPACT study, possibly due to the relative reluctance of patients to be randomized to chemotherapy\textsuperscript{(6)}, affected trial outcomes, with a survival signal seen only in the earlier-stage patient population. Finally, as discussed below, OS may be a more appropriate endpoint in clinical trials designed for immunotherapy.

Another recent and important study\textsuperscript{(7, 8)} tested an off-the-shelf vaccine that was developed at the National Cancer Institute and is composed of poxviral vectors (vaccinia prime with fowlpox boost) containing prostate-specific antigen (PSA) and 3 human T-cell costimulatory molecules known as PSA-TRICOM (PROSTVAC; Bavarian Nordic Immunotherapeutics). In this multicenter randomized, double-blinded, controlled, phase II study, men with...
minimally symptomatic or asymptomatic mCRPC (\(n = 125\)) who were treated with PSA-TRICOM had a 44% reduction in death rate (\(P = 0.006\)) and an 8.5-month improvement in median OS compared with patients treated with wild-type poxviral vectors (9). This hypothesis-generating study paved the way for a global randomized, controlled, phase III OS endpoint trial that is scheduled to start in 2011. It should be noted that the improved OS associated with therapeutic prostate cancer vaccines was not associated with the substantial treatment-related toxicity that is commonly observed with conventional cytotoxic chemotherapy (Table 1).

A third immunotherapeutic modality, ipilimumab, is currently in phase III trials in prostate cancer. This agent differs from the approaches described above in that ipilimumab does not function as a traditional vaccine. Instead, this fully human monoclonal antibody attenuates negative signals provided to T cells through the cell surface molecule CTLA-4, blocking a negative checkpoint (10, 11). Recent phase III data show that ipilimumab prolongs survival in patients with melanoma (12), and 2 phase III OS trials are investigating the activity of ipilimumab in patients with mCRPC. The first trial is combining radiation with either ipilimumab or placebo in the post-docetaxel setting (13), and the second is evaluating the activity of ipilimumab versus placebo in chemotherapy-naïve patients (14). Given the emerging enthusiasm for immunotherapy in prostate cancer, this article provides a timely review of recent advances in the field of immunotherapy for prostate cancer, lessons learned from early successes and failures, and areas requiring further study.

Endpoints

The clinical trials of sipuleucel-T and PSA-TRICOM described above demonstrated a statistically significant and clinically meaningful improvement in OS in patients with mCRPC. However, none of these studies showed an associated improvement in progression-free survival. In the context of traditional cytotoxic therapies, this apparent disconnect at first seems difficult to explain. However, it must be understood that a therapeutic cancer vaccine differs from conventional therapy in several distinct ways. First, its 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 (15). However, a vaccine can lead to the development of long-lived memory cells with the potential to supply continuing immunologic pressure, resulting in a slowing of the tumor’s net growth rate. In a tumor, new cells are constantly being produced while other cells are dying. The rate of tumor growth is thus influenced by tumor biology (e.g., formation of new daughter cells) offset by host biology (e.g., loss of tumor cells resulting from antitumor immune response), combined with factors introduced into the tumor environment (e.g., 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 (within 3–4 months) improvements in progression-free survival, but because this effect may be long-lasting and may be augmented by subsequent therapies (16, 17), improved OS may ultimately ensue. Indeed, recently published data from prostate cancer vaccine trials at the National Cancer Institute support the concept of decreased growth rate following a therapeutic vaccination (18). It is interesting to note that a recently published phase III trial of ipilimumab in metastatic melanoma (12) showed a similar lack of improvement in median progression-free survival but a statistically significant, clinically meaningful improvement in OS, suggesting that this effect may be typical of immunotherapies as a class.

This new understanding of the kinetics of a clinical response after a therapeutic vaccination, coupled with clinical experience showing that OS may be the only endpoint that can be a discriminator of activity in single-agent vaccine studies, poses a dilemma for investigators seeking to accelerate proof-of-concept studies. Because trials with a survival endpoint typically take years to accrue and mature, the ability to identify and validate intermediate endpoints is crucial to facilitate an efficient life cycle of phase II studies in prostate cancer, perhaps especially for immunotherapy studies. Circulating tumor cells (CTC) may be a reasonable biomarker for nonimmunotherapy studies (19); however, the altered kinetics of a clinical response following vaccination may have only a minimal impact on CTCs, at least in the short term. Although research into correlating cellular and humoral immune responses after vaccination with OS is ongoing, data from prospectively designed, controlled studies are currently insufficient to demonstrate the utility of such approaches.

Timing of Immunotherapy in the Treatment Pathway

If it is true that resetting the equilibrium of tumor growth rate leads to improved outcome, it follows that the earlier this equilibrium is reset, the greater will be the potential long-term survival benefit (Fig. 2). This concept is supported by data from a recently published phase II clinical trial of PSA-TRICOM (20), in which OS was compared with predicted survival based on a validated nomogram (5). For patients with a predicted survival of <18 months (about 50% of patients), the median OS of vaccine-treated patients exceeded the median predicted survival by about 2 months. However, for patients with a predicted survival of ≥18 months, the median OS of vaccinated patients had not yet been reached and will be ≥16 months longer than predicted. These data strongly support the concept that patients with earlier-stage disease benefit the most from treatment with PSA-TRICOM, and perhaps other immunothers as well.

Of interest, the median predicted survival in the IMPACT study and the multicenter PSA-TRICOM study was about 21 months, whereas the VITAL-1 trial comparing an allo-geneic whole tumor cell vaccine (genetically engineered to express GM-CSF) and docetaxel had a median predicted

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*a* Compared with comparator arm. NA, not approved.
survival of 16 months (6). In the latter study, there was a crossover in the curves, with an apparent survival advantage of receiving chemotherapy for patients destined to die earlier but an apparent advantage to receiving vaccine for patients who lived longer. In a retrospective analysis, patients with a predicted survival of ≥18 months showed a trend to improved OS when treated with a cell-based vaccine, compared with treatment with docetaxel. Also of note are the similar Kaplan–Meier curves of OS in these immunotherapy trials (Fig. 3). Multiple controlled studies have shown a delayed separation in the curves, with no evidence of benefit for immunotherapy in the first 6 to 12 months, indicating that the up to 15% to 25% of patients destined to succumb within that period of time gained no benefit from the vaccine (21). These data affected the decision to include only patients with a life expectancy of ≥12 months in the planned phase III trial of PSA-TRICOM.

There is also a biological rationale for using therapeutic vaccines earlier in the disease process. Although more than a decade of research has shown that therapeutic vaccines can overcome immunologic tolerance and generate tumor-associated, antigen-specific T cells, in order to be active, these T cells must traffic to, recognize, and remain functional at the tumor site. However, as a tumor mass grows, its microenvironment becomes increasingly hostile to an effective immune response (22). Negative regulatory cytokines such as TGF-β and interleukin (IL)-10, are expressed, making the tumor a haven for regulatory T cells (Tregs) and myeloid-derived suppressor cells. Another immunologically relevant molecule found in tumors is indoleamine 2,3-dioxygenase (IDO), an inducible enzyme involved in tryptophan catabolism. The depletion of tryptophan in tumors by IDO decreases the functionality of effector T cells and causes dendritic cells to become immunosuppressive (23). Tumors also may downregulate MHC molecules, depriving antitumor T cells of a means of recognizing these cells (24). Thus, tumor size may reach a tipping point beyond which therapeutic vaccines may be ineffective as a single modality. It is possible that for larger or more aggressive tumors, combination immunotherapy might be required to achieve an optimal antitumor response.

Combination Immunotherapy

In clinical oncology, very few metastatic cancers are currently treated with single-agent chemotherapy. Indeed, combination chemotherapy can be curative for patients with testicular cancer and a number of hematologic malignancies. Thus, it seems natural to assume that combination immunotherapy might also hold clinical promise. In this regard, prostate cancer is unique among solid tumors in that initial treatment with androgen ablation is nearly universally successful (25). Surprisingly, androgen ablation is not an immunologically neutral manipulation. Several studies have shown that chemical castration results in a profound influx of activated immune cells into the prostate gland (26, 27), a mitigation of prostate-specific T-cell tolerance (28), and thymic regeneration accompanied by the output of new T-cell specificities (29). Preclinical (30) and clinical (31) studies support this concept, but large-scale clinical testing of combined hormonal/immunotherapeutic approaches in androgen deprivation-naïve patients is complicated by the relatively long time horizon required for a definitive (survival or time to metastasis) endpoint. One solution to this difficulty might be to restrict enrollment to patients with more aggressive disease (e.g., higher Gleason score, more rapid PSA doubling). However, these aggressive tumors may be precisely the subset in which immunotherapy is less likely to be effective.

Because docetaxel chemotherapy every 3 weeks with daily prednisone is currently the standard of care for men with mCRPC (32–34), combinations of chemotherapy and immunotherapy might be considered as well. Patients given lower, more frequent doses of docetaxel...
The lymphodepleting properties of chemotherapy, as well as by standard clinical practice, in which docetaxel is administered with continuous corticosteroids. These immunosuppressive effects may be at least partially offset by the homeostatic proliferation of T cells that occurs after chemotherapy (36), as well as by additional proinflammatory phenomena such as Treg depletion (37, 38), augmentation of vaccine-specific immune responses (39), and antigen release (40). One way to sidestep these issues might be to sequentially combine immunotherapy and chemotherapy by administering immunotherapy before chemotherapy, in part to avoid the immunosuppressive effects of chemotherapy, but also to engender a proinflammatory microenvironment in which tumor-cell destruction by chemotherapy can be augmented by immune-mediated lysis. This approach will be formally evaluated in a recently opened Eastern Cooperative Oncology Group trial (E1809) comparing chemotherapy alone with PSA-TRICOM followed by chemotherapy.

A more innovative approach to combination immunotherapy would be to pair 2 or more immunotherapeutic agents, such as a vaccine to stimulate T-cell proliferation and a checkpoint blocking agent to attenuate negative regulation. In prostate cancer, the immune checkpoint blocking agent anti-CTLA-4 (ipilimumab) has been combined with both PSA-TRICOM (41) and a GM-CSF-secreting whole tumor cell vaccine (GVAX; BioSante Pharmaceuticals). Neither study has been fully reported yet; however, preliminary results are encouraging. Such studies have traditionally used the 2 agents simultaneously, but it is not clear that this approach gives optimal clinical results. In terms of immune checkpoints, recent data suggest that the checkpoint mediated by programmed death (PD)-1 (42) may prove to be an even more suitable target than CTLA-4 for prostate cancer immunotherapy, as the majority of CD8 cells that infiltrate the gland appear to express this target (43). Furthermore, recent clinical studies suggested that PD-1 blockade has a more benign toxicity profile than CTLA-4 blockade (44).

Although OS has been the only endpoint to demonstrate clinical benefit in clinical trials of therapeutic vaccine alone in prostate cancer, it is possible that combination studies of therapeutic vaccines with other modalities may lead to earlier discriminatory endpoints, such as time to progression or PSA response, which could accelerate proof-of-concept (phase II) studies.

**Sequencing Immunotherapy with Other Treatment Modalities**

Despite the enthusiasm for combinatorial approaches, the only FDA-approved immunotherapy currently available for the treatment of prostate cancer is sipuleucel-T. This agent is currently approved for men with asymptomatic or minimally symptomatic mCRPC (45). Although ~20% of men enrolled in phase III trials of sipuleucel-T had been previously treated with docetaxel chemotherapy, it seems likely that, in general, immunotherapy will be
administered prior to chemotherapy and thus early in the disease course. This straightforward treatment paradigm may soon be complicated by FDA approval of the novel hormonal agent abiraterone. This interesting drug, a 17-
lyase inhibitor (46, 47), inhibits both adrenal and intra-
tumoral steroid hormone synthesis, resulting in clinical responses in both prechemotherapy (48) and postche-
motherapy (49) settings. Should abiraterone be FDA-
approved, 2 issues will arise regarding the sequencing of this agent with sipuleucel-T. The first is whether abiraterone should be administered before or after sipuleucel-T. Because preclinical data suggest that immunotherapy may be optimally effective when administered before androgen ablation (30), a sequence of sipuleucel-T followed by abiraterone acetate might seem logical. However, it must be recognized that such a sequence has not been formally evaluated in terms of either clinical or surrogate immunologic endpoints. Of more importance, the registra-
tion trials of abiraterone acetate have administered this agent with moderate doses of corticosteroids (i.e., predni-
sone 10 mg/d) to mitigate symptoms of compensatory mineralocorticoid excess. This practice raises the question as to whether long-term use of immunosuppressive corti-
costeroids will attenuate the clinical benefit (i.e., increased survival) provided by sipuleucel-T. It is important to note that it is not universally agreed that corticosteroid use is absolutely required when abiraterone acetate is adminis-
tered in the prechemotherapy setting (50, 51). Thus, a reasonable approach to sequential administration of immunotherapy and abiraterone acetate might be to administer immunotherapy first and then treat with abir-
aterone acetate in the absence of corticosteroids, if possible. Although some data suggest that corticosteroids do not blunt responses to influenza vaccine in children (52) or in pulse doses in combination with a therapeutic cancer vaccine (35), daily use with vaccine has never been tested. Considering that memory T cells may be relatively spared compared with naïve T cells once steroids have been introduced, therapy that includes daily glucocorticoids should ideally be initiated after enough time has elapsed to generate a memory response, generally at least 3 to 4 weeks after the last therapeutic vaccine. If it is clinically warranted, a longer period may further preserve an immune response. Given the use of glucocorticoids with prostate cancer chemotherapy (docetaxel, cabazitaxel, and mitoxantrone), this has implications for immunotherapy followed by chemotherapy as well. However, definitive testing of this sequential approach clearly requires exploration in appropriate, well-designed, adequately powered clinical trials.

Controversies

With approval of a new class of agents, areas of contro-
versy often emerge. In addition to the notion that immu-
notherapy approaches can lead to improved OS without quantifiable differences in time to progression, several additional issues regarding sipuleucel-T should be discussed. Perhaps first among these is cost. Sipuleucel-T costs $93,000 per patient for a complete course of treatment (over about 1 month). Compared with the cost of docetaxel infusion, this cost may seem exorbitant. However, if one considers the total costs of docetaxel chemotherapy, including infusion, potential hospitalizations, and the use of growth factors, the overall cost for 6 to 8 months of che-
motherapy (a typical treatment course) may approach that of sipuleucel-T ($45,000 to $60,000; ref. 53). Of course, this analysis does not take into account the substantially reduced side effects of immunotherapy relative to chemotherapy or the cost of lost work due to multiple scheduled visits and potential hospitalizations. A second issue, as previously discussed, is the impact of age on immune response. To date, the IMPACT study has provided the only appropriate data for evaluating the effect of age on a patient’s ability to mount an immune response. In this study, the relative benefit of sipuleucel-T in terms of OS was the same in patients below and above the median age (4). Some inves-
tigators have argued that reinfusion of the control arm with only a third of the cells obtained by apheresis (to allow for eventual manufacture of active vaccine for crossover) led to relative immunosuppression in that cohort, which may explain the differences in outcome. However, several facts argue against this notion. First, although up to 50% of circulating lymphocytes may be removed during apheresis, this represents <1% of the total body lymphocyte pool—a clinically and immunologically insignificant percentage (54). In addition, there were no differences in infection rate between the 2 arms, confirming a lack of meaningful immunosuppression in the control arm.

Conclusions

Prostate cancer may seem a surprising choice as the target for the first FDA-approved therapeutic immunotherapy, given the relatively greater amount of investment in immu-
notherapy for melanoma and renal cell cancer. The approved agent, sipuleucel-T, is generally well tolerated and provides a clinically meaningful survival benefit. How-
ever, studies have not reported other short-term indicators of clinical benefit, such as time to progression and PSA responses, and trials of several other agents seem to support the notion that the only reliable endpoint for clinical trials of immunotherapy for prostate cancer is OS. This creates a less than optimal clinical scenario in which a long period of time is required for trials to mature. Complicating the issue is the generally accepted notion that immunotherapy should be administered early in the disease course, when it is most likely to benefit patients with minimal tumor burden. Current clinical practice reflects these considerations, and immunotherapy is com-
monly administered prior to cytotoxic chemotherapy. The pending incorporation of novel hormonal therapies into the clinical compendium raises interesting questions regarding the optimal sequencing of immunotherapy and hormonal therapy—questions that are best addressed by appropriate clinical trials. Perhaps the most exciting
concept to arise from recent trials is the use of combination immunotherapy, involving either multiple immunoagents or immunotherapy combined with conventional treatments. Although such trials raise additional questions about sequential versus simultaneous administration, preclinical data overwhelmingly suggest that combination approaches could lead to major advances in clinical benefit.

Disclosure of Potential Conflicts of Interest

Dr. Drake has served as a paid consultant for Dendreon and Bristol-Myers Squibb (BMS) and is a co-inventor for a patent licensed to BMS. No potential conflicts of interest were disclosed by Dr. Gulley.

Acknowledgments

The authors thank Jeffrey Schlom for his insightful comments, and Bonnie L. Casey for her editorial assistance in the preparation of this manuscript.

Grant Support

Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health (J.L. Gulley); and National Institutes of Health (B01 CA127113 and 1F50CA8826–15), Patrick C. Walsh Fund, OneInDox Foundation, and Prostate Cancer Foundation (C.G. Drake). C.G. Drake is a Damon Runyon–Lilly Clinical Investigator.

Received January 7, 2011; revised March 18, 2011; accepted April 19, 2011; published online June 16, 2011.

References


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*Clin Cancer Res* 2011;17:3884-3891.

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