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Update: Immunological Strategies for Prostate Cancer

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Abstract

Prostate cancer is the second most common cause of cancer-related death in US men. Along with initial therapy using surgery, radiotherapy, or cryotherapy, hormonal therapy is the mainstay of treatment. For men with advanced (metastatic) disease, docetaxel-based chemotherapy is US Food and Drug Administration (FDA)-approved, and provides a significant survival advantage. This relative paucity of treatment options drives an ongoing quest for additional treatment modalities; among these is immunotherapy. The concept that prostate cancer is a malignancy that can be targeted by the immune system may seem counterintuitive; certainly kidney cancer and melanoma are more traditionally thought of as immune responsive cancers. However, prostate cancer arises in a relatively unique organ and may express a number of proteins (antigens) against which an immune response can be generated. More importantly, several of these agents have now demonstrated a significant survival benefit in randomized controlled clinical trials, and one agent in particular (Sipuleucel-T, Dendreon Corporation, Seattle, WA) could be FDA-approved in 2010. This update summarizes recent clinical developments in the field of prostate cancer immunotherapy, with a focus on dendritic cell vaccines, virus-based vaccines, DNA-based vaccines, and cell-based vaccines. In addition, the notion of agents that target immune checkpoints is introduced. Enthusiasm for prostate cancer immunotherapy is founded upon its potential to mediate targeted, specific, tumor cell destruction without significant systemic toxicity; however, this has yet to be fully realized in the clinical arena.

Keywords

Immunotherapy; Immune checkpoints; Prostate cancer; T cell; Vaccine; CTLA-4; PD-1; GVAX; ProstVac VF; Sipuleucel-T

Introduction

Cancer immunotherapy refers generally to approaches that attempt to treat cancer by activating an immune response directed against tumor cells while overcoming tumor-

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induced tolerance. Although prostate cancer has not traditionally been thought of as a disease amenable to immunological therapies, this concept has recently been challenged for several reasons. First, prostate cancer is a slow-growing disease that may give a stimulated immune system time to generate an antitumor response while overcoming immunosuppressive factors. Second, recent evidence suggests that prostate cancer is more immunogenic that previously thought, having the ability to induce spontaneous autoantibodies [1]. Third, both proteomic and microarray analyses have identified several relatively tissue-specific proteins that may serve as prostate tumor antigens. Finally, abundant laboratory data suggest that antitumor immune responses can be elicited against prostate cancer cells, especially when active immunotherapy is combined with approaches that mitigate tolerance (eg, immune checkpoint blockade, androgen ablation, or radiotherapy). For these reasons, and because of the relative safety of immunotherapy, there are currently multiple immunological strategies in clinical development for prostate cancer (Table 1). The most recent developments in this field are reviewed here.

Methods

A PubMed search for English-language manuscripts related to prostate cancer immunotherapy was conducted. As specified by journal guidelines, only recent articles (within the past 2 years) were reviewed. This update focuses primarily on agents and approaches that are being tested in a clinical trial setting. Several interesting trials, both completed and in progress, are discussed, with a particular emphasis on innovative and/or emerging immunological concepts.

Dendritic Cell Vaccines

The most significant clinical trial result during the review period involves an agent that utilizes the patient's peripheral blood monocytes, harvested via leukapheresis, to create a "personalized" immunotherapy product known as Sipuleucel-T (Provenge, Dendreon Corporation, Seattle, WA). In this approach, cells are cultured with a proprietary protein cassette, a fusion protein between the target antigen (prostatic acid phosphatase [PAP]) and granulocyte monocyte colony stimulating factor (GM-CSF) [2]. Mechanistically, GM-CSF is intended to activate and mature monocytes toward dendritic cells, which present their target antigen to T lymphocytes in a stimulatory context. Activated T lymphocytes then traffic widely throughout the body, theoretically recognizing and killing tumor cells through a variety of nonredundant molecular programs. The target antigen PAP was chosen based on interesting preclinical animal studies [3], which showed that a PAP-targeted vaccine could break tolerance in intact animals, inducing significant prostatitis in intact hosts. Compared with other immunotherapy platforms, this approach has the theoretical advantage of removing the patient's cells from their endogenous, tolerogenic environment during stimulation. In addition, prostatic antigen represents a unique target protein against which immune responses can be quantified using a variety of methods.

Several clinical trials using this agent have been published, with initial studies demonstrating safety and suggesting some degree of efficacy [4]. Encouraging results have come from a trial performed in patients with metastatic castrate-resistant prostate cancer

(CRPC) who were either asymptomatic or mildly symptomatic. In this trial, Sipuleucel-T (three doses 2 weeks apart) was compared with placebo, with a 2:1 randomization in favor of the immunotherapy arm. The results of this small (127 patient) phase III trial were reported in 2006 [5•]. Here, Sipuleucel-T showed a significant survival advantage versus placebo (25.9 months vs 21.4 months; P=0.01). Because overall survival was not the primary end point of this study, and the trial was rather small relative to typical phase III trials in prostate cancer, those results were not universally persuasive. In 2007, a larger (526 patient) trial with a nearly identical design completed enrollment, and phase III data were first presented in 2009 [6••]. The results of the larger trial were consistent with earlier studies, showing a 4.1 month survival advantage for Sipuleucel-T immunotherapy compared with placebo, translating to a 22% relative reduction in the risk of death. The corresponding biological license application was amended in late 2009, and a US Food and Drug Administration (FDA) decision regarding marketing is expected in the second quarter of 2010. Although the survival data in these trials appear robust and consistent, it should be noted that the comparator arm in each case was a placebo group, not chemotherapy using docetaxel, which has also been demonstrated to provide a survival advantage in men with CRPC [7, 8]. This comparison can be justified by the notion that chemotherapy for prostate cancer is in many cases reserved for men with later stage (symptomatic) disease, but that concept is not without controversy [9].

Virus-Based Vaccines

Cancer immunotherapy in general, and prostate cancer immunotherapy in particular, can be engineered using attenuated viral vectors. This approach has a long history, and has the advantage that viral vectors can be engineered to carry large payloads. In addition, and in contrast to the complexity of the cell-based approach described above, viral vaccines are also relatively easy to manufacture and distribute. The majority of the work in this area has focused on prostate-specific antigen (PSA) as the target antigen, with pox-viruses as the vectors [10•]. These vectors are generally quite efficient in priming an immune response. However, subsequent immunization results in responses more heavily directed against the viral backbone than against the encoded target antigen. Thus, a heterologous prime-boost strategy was investigated, in which vaccinia-based vectors were alternated with vectors based on a fowlpox backbone. In an important randomized clinical trial, it was determined that optimal immune responses were engendered when vaccinia-based vectors were used in the priming phase, followed by subsequent fowlpox boost [11]. Interestingly, long-term follow-up of this early trial recently suggested a survival advantage in men treated in the vaccinia prime/fowlpox boost arm, providing further support for the concept of a heterologous prime-boost strategy. This recombinant vaccinia-PSA (rV-PSA)/recombinant fowlpox-PSA (rF-PSA) combination was further modified by the addition of three well-characterized immune-stimulatory molecules to the vectors [12]. The final product (known as ProstVac VF) therefore includes rV-PSA and rF-PSA and also contains a triad of costimulatory proteins known as TriCom (intercellular adhesion molecule-1, B7-1, and leukocyte function-associated antigen-3). A large number of trials utilizing this agent—both alone and in carefully considered combinations—have been completed, and these data are nicely reviewed in a recent publication by Madan et al. [10•].

However, the most significant result in the development of ProstVac VF came only recently in the form of updated results from a clinical trial in which this agent was compared with placebo in a 125-patient randomized phase II trial in men with minimally symptomatic CRPC. This trial, designed similarly to the successful trials of Sipuleucel-T discussed above, was a 2:1 randomized study with a primary end point of progression-free survival. Initial analysis of this trial was less than encouraging, but as the data matured it became clear that there was a significant overall survival (OS) advantage associated with ProstVac VF treatment compared with placebo (median survival 21.5 versus 16.4 months; HR, 0.56; P=0.006) [13••]. However, these data must be viewed as hypothesis-generating, because OS was not the primary end point of the original trial. Commercial rights to ProstVac VF have been secured by Bavarian Nordic, and a phase III trial is under development. The results of this study are instructive in that they point out the potential importance of OS as a primary end point in clinical immunotherapy trials for men with prostate cancer, as well as the relatively extensive time periods required for data to fully mature. In that regard, a recently published retrospective analysis of an earlier ProstVac VF trial is particularly noteworthy. Here, the authors showed that the prostate cancer patients who benefit from immunotherapy appear to be those with a greater overall predicted survival as quantified by an application of the Halabi nomogram [14]. Although encouraging from the standpoint of patient selection, these data are also somewhat discouraging in terms of clinical development, confirming the concept that these types of clinical trials can potentially take several years to mature.

DNA-Based Vaccines

Prostate cancer immunotherapy based on administration of plasmid DNA has also been evaluated clinically, with an important trial result reported in 2009 [15•]. This platform is one of the most flexible and straightforward available, but this flexibility comes at a price because such constructs are generally less immunogenic than, for example, viral-based vectors. This relatively modest immunogenicity, coupled with the notion that the barriers to successful immunotherapy for prostate cancer may be less formidable in a minimal disease setting, led McNeel et al. [15•] to perform a phase I clinical trial of a DNA vector targeting PAP in men with early stage (biochemically recurrent) prostate cancer. As is typical for immunotherapy studies, very little toxicity was noted, but immune responses against the target antigen could be demonstrated. There was also a suggestion that the PSA doubling time of treated men increased (corresponding to a slowing of the rate of PSA rise), but it is generally acknowledged that the clinical significance of such changes is uncertain at the present time. The relative ease with which DNA-based vaccines can be constructed is encouraging; the vector used in this vaccine can theoretically be employed to compare several potential target antigens in a head-to-head manner.

Cell-Based Vaccines

Because cancer cells themselves are generally nonimmunogenic, antitumor immunity may be induced by intradermal injection of cancer cells engineered to express a proinflammatory cytokine [16]. An agent known as prostate GVAX embodied this approach in the clinic. Prostate GVAX consisted of two allogeneic prostate cancer cell lines (PC3 and LNCaP), genetically modified to secrete GM-CSF [17]. This whole-cell approach had several theoretical advantages, most notably that of presenting a large number of tumor antigens

simultaneously. Based on encouraging phase II data [18, 19], two large randomized phase III studies of GVAX immunotherapy (VITAL-1 and VITAL-2) were initiated in 2004 and 2005, respectively. VITAL-1 enrolled 626 men with asymptomatic chemotherapy-naïve CRPC, and randomly assigned them to prostate GVAX or docetaxel/prednisone [20•]. VITAL-2 was expected to enroll 600 patients with symptomatic metastatic CRPC, randomly assigning them to standard docetaxel/prednisone or docetaxel/GVAX. The primary end point of these trials was OS, but both studies were terminated early. VITAL-1 was closed because data from an unplanned interim analysis suggested that an OS benefit was unlikely to be realized. VITAL-2 was terminated because of an apparent increase in deaths in the docetaxel/GVAX arm. The mechanism for this imbalance in deaths has not been fully explained, but did not seem to result from excess toxicity in the immunotherapy arm. As was the case in the ProstVac VF trial discussed above, it remains theoretically possible that longer follow-up of VITAL-1 could reveal a late treatment effect of GVAX. However, further commercial development of this platform has been discontinued by the manufacturer.

Immune Checkpoints

As is clear from the discussion above, much of the work in prostate cancer immunotherapy revolves around the concept of “vaccination,” in which a prostate cancer-associated antigen (or antigens) is introduced into a tumor-bearing patient in an effort to engender, or perhaps boost, an antitumor immune response. The principal obstacle to such approaches is obvious. In sharp contrast to vaccines used to prevent infectious diseases, prostate cancer patients have coexisted with their tumors for several years. Thus, the tumor and its associated stroma have evolved multiple mechanisms by which to evade immune attack [21]. Although a comprehensive discussion of these multiple escape mechanisms [22] is clearly beyond the scope of this update, the mechanism of immune checkpoints is worthy of mention because agents targeting such checkpoints have advanced to the point of phase III trials in men with prostate cancer. These checkpoint molecules are expressed on the cell surface of cancer-specific CD4 and CD8 lymphocytes, their expression serving as an effective “brake” to impede an antitumor response. In a normal host, these checkpoints most likely serve to attenuate autoimmunity, preventing the organism from damaging self-tissues as a result of an overly exuberant immune response. Tumors have co-opted this mechanism, and prostate cancer-infiltrating lymphocytes appear to express a number of such molecules, most notably cytotoxic lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) [23].

A monoclonal antibody specific for CTLA-4 (ipilimumab) has been extensively evaluated for patients with metastatic melanoma. In this setting, it has a reasonable response rate (approximately 10%) but, as expected, is associated with a nontrivial incidence of immune-related adverse events of grade III and IV severity [24]. This agent has been the subject of a number of early phase trials in prostate cancer, with several PSA declines reported [25•, 26•]. These results are particularly noteworthy, because *bona fide* PSA responses were rarely reported in the active immunotherapy (vaccine) trials discussed above. Ambitiously, a randomized phase III trial of this agent has recently been initiated in patients with prostate cancer. In contrast to many of the trials mentioned above, this study targets men with end-stage disease, that is, those with metastatic CRPC who have not responded to chemotherapy.

The rationale for the choice of this patient population is that there is currently no standard approved treatment that provides a reliable survival advantage after docetaxel failure [27]. This trial is somewhat innovative in that it includes low-dose radiotherapy prior to immunotherapy in an effort to prime an antitumor response through release of antigen from irradiated tumor cells. In addition to ipilimumab, a monoclonal antibody targeting the immune checkpoint mediated by PD-1 (MDX-1106, Bristol Myers Squibb, New York, NY) is also in early-stage clinical trials. Although such trials include a number of patients with prostate cancer, a prostate cancer-specific trial has not yet been initiated.

Conclusions

The review period covered by this report represents a promising era for prostate cancer immunotherapy. Two randomized clinical trials using very different agents (Sipuleucel-T and ProstVac VF) independently demonstrated a statistically significant survival advantage over placebo in patients with metastatic CRPC. Significantly, the former trial may provide the basis for regulatory approval of Sipuleucel-T. In addition, smaller studies have provided clinical support for the notion that immunotherapy is most likely to be effective in men with less advanced disease, and have introduced the concept of DNA-based vaccination as an interesting and flexible platform. Perhaps most intriguingly, the concept of immune checkpoint blockade is emerging as an alternative to traditional vaccination approaches, with a large randomized phase III study using ipilimumab currently underway. In the future, it seems likely that clinical combinations of active immunotherapy with immune checkpoint blockade, or perhaps combinations involving conventional therapy in series or parallel with immunotherapy, may result in more effective treatment for men with prostate cancer.

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Table 1

Selected immunotherapies for prostate cancer

Agent	Mechanism/Target	Furthest clinical development
Immunotherapy		
Sipuleucel-T	Autologous PAP-loaded dendritic cell-based immunotherapy	Phase III trials completed, BLA filed
ProstVac VF	PSA-encoding poxviral vaccine	Randomized phase II trials completed; phase III planned
pTVG-HP	PAP-encoding DNA vaccine	Phase I/II trial completed
GVAX	Allogeneic GM-CSF-secreting tumor cell-based immunotherapy	Phase III trials terminated
Checkpoint inhibitors		
Ipilimumab	Fully human anti-CTLA-4 monoclonal antibody	Phase II trials completed; randomized phase III trial underway
MDX-1106	Fully human anti-PD-1 monoclonal antibody	Phase I trial completed; phase Ib trial underway

BLA biological licensing application; *CTLA*-4 cytotoxic lymphocyte antigen 4; *GM-CSF* granulocyte monocyte colony stimulating factor; *PAP* prostatic acid phosphatase; *PD*-1 programmed death-1; *PSA* prostate-specific antigen