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Update on Prostate Cancer Vaccines

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Abstract

The recent FDA approval of Sipuleucel-T (Dendreon, Seattle WA) for the treatment of men with asymptomatic or minimally symptomatic castrate resistant prostate cancer was a landmark in cancer immunotherapy, making this the first cancer “vaccine” approved for use in a treatment setting. This approval has led to renewed interest in cancer vaccines, and to the recognition that prostate cancer represents an immunologically sensitive disease. At the current time, several vaccine approaches are under clinical investigation. These include viral vectors, antigen-loaded dendritic cells, and DNA vaccines. Each approach has its own set of advantages and disadvantages. This review will introduce the basic technology underlying these different vaccines, and briefly discuss completed and ongoing clinical trials. As a great number of prostate cancer vaccines have been investigated in both preclinical and clinical settings, we will focus primarily on vaccines that are currently in clinical trials, as ascertained by a recent inquiry of the clinical trials database www.clinicaltrials.gov.

Keywords

prostate; vaccine; lymphocyte; dendritic cell; GM-CSF

Introduction

Prostate cancer is the most commonly diagnosed non-melanoma malignancy in the United States, with a lifetime incidence of approximately one in six(1). Initial (primary) therapy involves either surgery, radiation therapy, or hormonal therapy – although recent studies suggest that carefully selected men with low-grade disease may be carefully observed over time(2). About one third of patients treated with primary therapy eventually develop recurrent disease, usually presenting as a rise in the serum level of prostate specific antigen (PSA). Recurrent disease is slowly progressive, with a median time from PSA rise to detectable metastases of approximately seven years(3), and a median survival over ten years. This protracted disease course may permit sufficient time for an immune response to develop after vaccination, and also enables the repetitive vaccination schedules that might be required for an optimal anti-tumor immune response.

Dendritic Cell Based Vaccines

Sipuleucel T

Description—In 2010, the FDA approved Sipuleucel T (Dendreon, Seattle, WA) for the treatment of men with either asymptomatic or minimally symptomatic metastatic, castrate-

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DISCLOSURES

CGD has consulted for Dendreon Inc and BMS, Inc.

resistant prostate cancer (mCRPC). This approval, based on a blinded, randomized controlled trial, represented the first vaccine approved to treat established cancer of any type(4). Development of this platform, however, began almost 15 years earlier, with the demonstration that immunization of male rats with rat or human prostatic acid phosphatase (PAP) in Complete Freund's Adjuvant (CFA) resulted in autoimmune, lymphocyte-mediated prostatitis(5). These findings were important, demonstrating that tolerance to this particular prostate-restricted protein was not centrally mediated, and that vaccination could induce an immune response against a so-called self protein from the prostate gland. To translate this approach to the clinic, a modified dendritic cell vaccine platform was developed. Here, a patient's peripheral blood leukocytes are harvested via leukapheresis, then monocytes enriched via buoyant density centrifugation. To generate the vaccine product, these enriched monocytes are incubated for approximately 36 hours with a unique fusion protein which couples the target antigen (PAP) to the cytokine GM-CSF. In this platform, GM-CSF most likely serves to traffic the target antigen to receptors on dendritic cell (DC) precursors, which then present peptides from PAP on their cell surface in a context sufficient to activate specific CD4 and CD8 T cells. Activated, PAP-presenting DC thus serve as the "vaccine"; and the goal is the generation of a specific anti-PAP immune response. It should be noted, though, that the final product infused into patients contains other cell types as well, and that the inclusion of these additional cell types may be important in the potency of this product. Potential advantages of this approach include the ex-vivo DC maturation step; multiple studies show that DC within cancer patients are deficient in both number and function(6). In addition, the vaccine is administered three times at two week intervals, leading to increased immune activation of the infused product over time. The major disadvantage of Sipuleucel-T is the complexity involved in its manufacture, involving shipping the leukapheresis product to a central processing facility, ex vivo culture, and then shipping the finished product back to the treatment center for infusion.

Clinical Development/Ongoing Trials—Two Phase I trials showed that vaccination with PAP-loaded DC was generally well tolerated and that T cell responses to PAP could be detected post-vaccination(7;8). In one of these trials(7), several patients demonstrated a greater than 50% drop in serum PSA levels, suggesting clinical activity. A small randomized Phase III trial confirmed that finding(9). In that study (D9901), 127 patients with mCRPC were randomized 2:1 to active vaccination with Sipuleucel-T or to placebo. The primary endpoint of this study, progression free survival (PFS), was not met, but a planned secondary endpoint, median overall survival, showed a significant improvement in the treatment arm (25.9 months versus 21.4 months, HR 1.70, P = 0.01). These data were eventually confirmed in a pivotal phase III trial (D9902B). Here, 512 men with asymptomatic or minimally symptomatic mCRPC were once again 2:1 randomized to receive active vaccination versus placebo. Patients who subsequently progressed on the placebo arm were given the opportunity to participate in a salvage protocol in which active vaccine was manufactured from cryo-preserved PBL - a crossover to active treatment was possible. The primary endpoint of this trial, overall survival, was met with a survival of 25.8 months in the Sipuleucel-T group versus 21.7 months in the men initially treated with placebo (HR 0.77, P=0.02). While both clinically and statistically significant, these results were not without controversy, as the trial design could potentially lead to a slight delay in chemotherapy treatment in the control group. In addition, a secondary time to progression endpoint (TTP) was not met, raising interesting questions regarding the precise mechanism of action of this agent, i.e. how can one observe an increase in overall survival without radiological evidence of tumor response.

Multiple preclinical and clinical studies support the concept that tumor vaccines may function optimally in patients with a decreased tumor burden(10). Thus, now that FDA approval has been secured, one obvious developmental pathway for Sipuleucel T would be

to explore efficacy in men with earlier stages of prostate cancer. In particular, men with biochemically recurrent but non-metastatic prostate cancer are often treated with androgen ablation, an intervention with well-documented anti-tumor immunological effects(11–14). Combining androgen-ablation with prostate cancer vaccines would therefore seem a logical proposition. However, it is not clear whether the optimal therapeutic sequence is to vaccinate prior to, or after androgen ablation(15). A clinical trial exploring Sipuleucel-T in this context was recently announced(16). Here, men with biochemically recurrent prostate cancer will receive either androgen ablation followed by Sipuleucel-T, or the two agents in the opposite order. The primary endpoints of this randomized trial are immunological, the eventual goal being an future interventional trial comparing the optimal combination regimen to androgen ablation alone.

Tumor-mRNA Transfected Dendritic Cells

Description—Since activated dendritic cells are the most potent immune cell in terms of initiating an adaptive immune response(17), they represent an attractive platform upon which to base cancer vaccines(18). Ex vivo generation of such cells is relatively straightforward, involving the maturation of PBMC in the presence of certain cytokines (usually IL-4 and GM-CSF). To make a cancer vaccine, dendritic cells are loaded with antigen, and then matured to maximize antigen presentation to T and potentially B cells. The source of tumor antigen in these vaccines is important, and may involve synthetic peptides, autologous tumor cell lysates or lysates from cultured cancer cells. Using autologous tumor cell lysates is a particularly attractive option, as immunization is thus directed against the antigen repertoire derived from a patient's own individual tumor. But autologous cells vary greatly in number, viability and recovery, and require a sufficient surgical sample for vaccine to be made. Some of these issues may be circumvented by using cancer cell lines cultured in vitro, but the expression profile of such allogeneic cells may or may not intersect with the the antigens present in the patient's cancer. Some recent work in this area focusses on using tumor cell derived mRNA to transfect cultured dendritic cells – this approach can be standardized by extracting sufficient quantities of mRNA from cultured tumor cells(19), and has shown preclinical evidence of efficacy in animal models. Overall, the advantages of this approach include the presentation of a broad spectrum of antigens, as well as a potential augmentation of the immune response conferred by the non-self MHC molecules present in allogeneic tumor cells. Disadvantages of this approach include a relative complexity of manufacture, especially the 5 – 7 days typically required to culture and mature D.C. ex vivo.

Clinical Development/Ongoing Trials—A phase I trial using autologous (patient-derived) D.C. transfected with mRNA from allogeneic prostate tumor cells was recently published (20). Here, patients with metastatic, castrate-resistant prostate cancer (mCRPC) were treated with four doses of D.C. transfected with mRNA from the prostate cancer cell lines LNCaP, DU145 and PC-3. The vaccine was well tolerated, and resulted in a decrease in the rate of PSA progression in 13 out of 19 treated patients. Immune responses (proliferation to transfected D.C) were documented, and seemed to correlate with PSA responses, although patient numbers were small. This work has recently been extended clinically in the form of an active Phase I/II trial using autologous tumor cells as an antigen source (NCT01197625).

Virus-Based Vaccines

ProstVac VF

Description—Another method to generate an immune response against a particular target antigen is to couple that antigen to a viral backbone – in these approaches the multiple viral proteins serve to initiate a potent immune response. The advantage of such approaches is

their immunogenicity, and the off-the-shelf nature of the ensuing construct, which does not need to be individually prepared for each patient. The major disadvantage of viral vaccine constructs is the complex nature of the viral backbone, which means that the majority of the immune response is targeted against the virus itself, rather than the target antigen. This property makes repeated dosing particularly challenging, and the immune response to subsequent vaccinations may rapidly neutralize response to the target antigen. To circumvent these limitations, the NCI group has added two significant innovations(21). In the first, immunogenicity of the standard vaccinia vector was dramatically improved by the addition of three immunomodulatory proteins (LFA-1, ICAM and B7-1)(22). Preclinical studies showed that this combination was strikingly synergistic in terms of generating a targeted immune response, and this technology was adapted for clinical development. The second modification of a standard vaccinia approach was the observation that heterologous prime boost regimens could be utilized, providing that a second viral backbone was employed. In terms of target antigen, this group chose Prostate Specific Antigen (PSA). This choice was based on several factors, including the notion that PSA is rather exclusively expressed by the prostate gland and by prostate cancer. PSA may also play a functional role; several studies showed that increasing PSA levels confer increasing pathogenicity(23). The major advantages of this methodology include the off-the-shelf nature of the vaccine vector, as well as the well-optimized nature of the technology. The relative disadvantages of this platform include the univalent nature of the targeted protein (PSA), although some clinical studies have suggested that spread of the immune response to prostate cancer antigens not originally targeted by the vaccine may occur (24).

ii. Clinical Development/Ongoing Trials—As the clinical development of ProstVac VF has recently been reviewed(25), only selected trials will be highlighted here. In terms of early development, one important early trial of vaccinia-PSA was that performed to determine the optimal sequencing of a heterologous prime/boost regimen. This trial was critical; it showed that a vaccinia-PSA prime, followed by a series of fowlpox-PSA boosts was more immunogenic than other regimens(26). A carefully considered series of combination trials followed, involving chemotherapy, radiation therapy and androgen ablation. Most recently, an important randomized Phase II trial of ProstVac VF was reported(27). This was a randomized phase II trial, similar in design to the pivotal trial of Sipuleucel T. Men with asymptomatic or minimally symptomatic metastatic CRPC were enrolled, and randomized 2:1 to treatment with either ProstVac VF or placebo. The primary endpoint of this trial was time to progression, and upon progression men were treated at their physicians' discretion – no crossover was permitted. While the primary endpoint was not met, long term follow-up showed a statistically significant improvement in overall survival for the treatment group(25.1 versus 16.6 months., HR = 0.56, P = .006). Since overall survival was a secondary endpoint in this study, those data must clearly be considered hypothesis generating rather than definitive. Nevertheless, the observed improvement in survival was sufficiently intriguing that the technology is now being commercially developed(Bavarian Nordic, Mountainside CA), and a Phase III registration trial is planned to open to accrual in late 2011 (NCT01322490). This international trial will randomize approximately 1200 men to either ProstVac VF, ProstVac VF with GM-CSF as an adjuvant, or to placebo. The primary endpoint of this study is overall survival. In keeping with previous results(10), enrollment will be limited to men with favorable prognostic characteristics.

Another ongoing trial involving ProstVac VF tests the hypothesis that vaccination can improve the clinical efficacy of a subsequent treatment modality, in this case chemotherapy. This notion is well-supported by preclinical data(28), but certain chemotherapy regimens are clearly more immunogenic than others. In this Eastern Cooperative Oncology Group (ECOG) trial, men with slowly progressing mCRPC are randomized to either standard

docetaxel based immunotherapy, or to a course of ProstVac VF (administered over 12 weeks) followed by standard chemotherapy. The primary endpoint of this study (NCT01145508) is overall survival, as suggested by the Phase II data described above. In addition, immune response and time to progression will be evaluated as secondary endpoints. This is a significant trial in that it represents a formal attempt to evaluate the effect that cancer vaccination may have on subsequent therapy, and in that sense is broadly applicable to other tumor types and vaccine approaches as well.

TroVax®

Description—The TroVax® vaccine platform was based on the identification of a cell surface glycoprotein (5T4) as a potential tumor-specific target in several cancer types, including colorectal, renal and prostate cancer(29). A vaccine against 5T4 was engineered by incorporating 5T4 into a viral vector, in this case Modified Vaccinia Ankara (MVA) – an alternative vaccine against smallpox generally used in immunocompromised hosts. Unlike the ProstVac VF vaccine described above, TroVax® does not include a heterologous prime boost, and does not include a series of co-stimulatory molecules. A phase III trial in patients with renal cell cancer did not result in improved survival as compared to placebo, but subgroup analyses did suggest an improved survival in patients with a favorable prognosis(30). Preclinical data suggest that this vaccine functions through a CD4 T cell and antibody mediated mechanism, and that CD8 T cells are not required for efficacy(31), rendering it somewhat unique from the other approaches discussed here. The primary advantage of this platform is the novel target antigen, which might be broadly applicable to multiple tumor types. The major disadvantages are the univalent nature of the vaccine construct, as well as a homologous prime-boost regimen.

Clinical Development/Ongoing Trials—An open-label Phase II trial in men with mCRPC as recently reported(32). Here, 27 men with progressive disease were treated, 13 with TroVax® alone, and 14 with a combination of TroVax® and GM-CSF. The agent was generally well tolerated, with few adverse reactions reported. Five patients in the combined treatment group showed a PSA decline, while none were noted in the TroVax alone group. Currently, this agent is being evaluated in a randomized phase II trial similar to the ECOG trial of ProstVac VF described above, comparing vaccination plus chemotherapy to chemotherapy alone in men with metastatic CRPC (NCT01194960).

Adenovirus/Prostate Specific Antigen

Adenoviral vaccines represent an additional vector suitable for targeting tumor antigens, and some preclinical data suggest that these vectors might be more immunogenic than vaccinia or canarypox based vaccines(33). A major challenge to adenoviral-based vaccines is the presence of pre-existing neutralizing antibodies resulting from prior environmental exposure, which can neutralize adenoviruses before a strong T cell response is generated. Interestingly, the Ratliff group found that incorporation of an adenoviral vaccine targeting PSA (Ad/PSA) in a gelfoam matrix (Pharmacia) permitted this vaccine to induce anti-PSA response even in the presence of high-titer antibodies(34). The advantages of this platform include the relative immunogenicity of the adenoviral vector; a relative disadvantage might be the variation in pre-existing antibody responses to adenoviruses in human patients.

Clinical Development/Ongoing Trials—A Phase I trial of Ad/PSA with or without Gelfoam matrix was recently reported(33). The agent was shown to be safe (the primary endpoint of the trial), and anti-PSA T cell responses were documented in the majority of treated patients. As is the case for several of the other vaccine trials described here, an increase in the rate of rise of PSA (PSA doubling time) was noted in approximately half of the patients treated. Interestingly, Gelfoam had a mixed immunological effect, and was

associated with a decreased percentage of anti-PSA antibody responses, but increasing T cell responses as well as PSA doubling times. Based on these data, two new phase II trials have been initiated and are currently recruiting. The first (NCT00583024) is a standard single-arm Phase II trial with the primary endpoint of PSA doubling time versus that prior to enrollment. The second, and perhaps more interesting trial will enroll men with biochemically recurrent disease, and randomize them to either Ad/PSA vaccine, or Ad/PSA vaccine plus androgen ablation – an intervention with multiple immunological effects as described above.

DNA Vaccines

Description

The concept that naked DNA, injected intramuscularly, could induce a meaningful immune response was first described several decades ago(35), and DNA-based vaccines have been evaluated in several cancer types, including breast, colon and prostate cancer(36). Generating such vaccines is relatively straightforward, especially when compared to the dendritic cell and other vaccine platforms described above. In general the target antigen is simply engineered into a suitable expression plasmid. Large scale manufacture is similarly straightforward, involving standard bacterial culture and DNA isolation technologies. These characteristics form the basis for the primary advantage of DNA vaccines over competing technologies; the ability to rapidly target different antigens. The primary disadvantage of DNA based vaccines is their relatively poor immunogenicity, especially as compared to the relatively potent DC and viral-based approaches described above. This weakness has been partially addressed by the incorporation of additional stimulatory molecules (such as TLR agonists) into DNA vaccine backbones, but their relatively weak immunogenicity remains a major challenge to the development of DNA vaccines for prostate cancer. Preclinical data have recently been summarized(36), and are mostly remarkable for the wide variety of target antigens that have been evaluated, including PSA, prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP), prostate stem cell antigen (PSCA) and six transmembrane epithelial antigen of the prostate (STEAP).

Clinical Development/Ongoing Trials

An important Phase I trial of DNA vaccination in prostate cancer was recently reported(37). Here, the target antigen was PAP, and patients with early stage (biochemically recurrent, non-metastatic, disease) were enrolled. The DNA vaccine dose was escalated, and the vaccine was administered along with GM-CSF. Anti-PAP T cells and proliferative responses were detected in several patients, and there was a suggestion of increased PSA doubling times. This trial clearly demonstrated the feasibility of this approach, setting the stage for future clinical work. Two ongoing trials are underway, the first (NCT01341652) formally evaluates the role of GM-CSF by comparing DNA-PAP vaccination with GM-CSF to GM-CSF alone in men with biochemically recurrent (non-metastatic) disease. The second trial (NCT00849121) formally evaluates the role of boost vaccinations for this vector, comparing a fixed 12 week boost schedule to variable and more frequent boosting, based on immune response measurements. This second trial is especially interesting in that vaccination schedules are rarely formally optimized in a clinical, treatment setting.

Cell-Based Vaccines

(GVAX Prostate)

Description—The development of this vaccine technology was based on the seminal finding that transduction of cancer cells with the cytokine GM-CSF allowed such cells to function as a potent anti-cancer vaccine in a prevention setting(38). Generally, allogeneic

cell lines have been transduced, and the platform has been clinically evaluated in a number of cancer types, including lung, breast, pancreatic and prostate cancer(39). For prostate cancer, two cell lines (LNCaP and PC3) have been utilized, thus including both an androgen-sensitive, and an androgen-resistant cell line in order to provide broad antigen coverage.

Clinical Development—Clinical evaluation of GVAX prostate proceeded to the stage of two randomized Phase III trials. The first of these trials (VITAL-1) compared GVAX prostate to standard chemotherapy (docetaxel) for men with metastatic CRPC. In the second trial (VITAL-2), a combination of GVAX prostate and docetaxel was compared to docetaxel alone; this time a more advanced population, men with symptomatic mCRPC, was enrolled. Unfortunately, safety concerns led to the discontinuation of the second trial, with preliminary results suggesting an imbalance in deaths in the combined treatment group(40). Subsequent follow-up showed those safety concerns to be unfounded, with no statistical difference in mortality between groups. Nevertheless, these concerns prompted an unplanned, and slightly underpowered efficacy analysis of the VITAL-1 trial(41), which indicated futility, leading to the closure of that trial as well. The intellectual property rights to the GVAX platform have been transferred to BioSante Inc, and current clinical development in prostate cancer involves a planned neoadjuvant study in high-risk men (C. Drake, personal communication). Ongoing development in other tumor types (melanoma, breast and pancreatic cancer) is robust, with multiple combinatorial trials currently enrolling patients.

Conclusions

The pivotal Sipulecel T trial (D9902B)(4), and the randomized Phase II trial of ProstVac VF in a nearly identical patient population(27) provide strong evidence that immunotherapy (“vaccination”) can result in a survival benefit in advanced prostate cancer. This is surprising, as it might have been predicted that vaccines for the so-called immunogenic tumors (melanoma and renal cell cancer) might have been approved earlier. That has not been the case, as a number of trials in those diseases have not been successful in the Phase III setting(42). The precise immunological mechanisms underlying these differences are not clear but might relate to the notion that the prostate gland (at least in the absence of cancer) is immunologically ignored(12), leading to the potential availability of T cells that have not been centrally deleted to be recruited into the immune response. A second relevant mechanism may involve androgen-ablation; the vast majority of patients with prostate cancer treated with vaccines have been castrate, a physiological state associated with increased immune responsiveness through a number of mechanisms(13). Future studies will undoubtedly involve earlier application of vaccines, although the relatively long survival of men with prostate cancer makes registration trials in those earlier disease states daunting. Perhaps most exciting is the notion of combining vaccination with monoclonal antibodies blocking immune checkpoints such as CTLA-4(43), PD-1(44) or with stimulatory antibodies like anti-41-BB(45). Indeed, the tripartite combination of standard cancer treatment regimens that minimize tumor burden, immune checkpoint blockade, and finally cancer vaccination may ultimately be required for optimal clinical benefit.

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Table 1

Summary of Prostate Cancer Vaccines Currently in Clinical Development

Agent	Advantages	Disadvantages	Stage of Development
Sipuleucel-T	FDA Approved (survival benefit) Ex-Vivo DC culture may circumvent tolerance	Complex manufacturing process Monovalent	Post-Approval
mRNA Transfected DC	Polyvalent Potency of optimally engineered DC	In vitro culture required	Phase II
ProstVac VF	Optimized viral platform Heterologous prime-boost regimen Off-the shelf product	Monovalent	Phase III in planning phase Combinatorial Phase II trials ongoing
TroVax®	Unique antigen May be applicable to multiple tumor types	Relatively simple platform (MVA) Monovalent	Combinatorial Phase II trial in progress
Ad/PSA	Immunogenicity of adenoviral platform Gelfoam formulation may circumvent pre-existing antibody response	Pre-existing antibodies may modulate efficacy Monovalent	Two Phase II trials in progress
DNA – PAP	Flexible platform may allow screening of various antigens Flexible platform may allow for incorporation of additional stimulatory molecules	Relatively poor immunogenicity	Two Phase II trials in progress
GVAX Prostate	Polyvalent with broad spectrum of potential antigens Generally safe in large Phase III trials Standard cell culture for manufacture	Potentially poorer expression of any given antigen Discontinued Phase III trials dampen enthusiasm	Neoadjuvant trial in development