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Immunotherapy for metastatic prostate cancer

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Abstract

Chemotherapy with docetaxel is the standard treatment for men with metastatic prostate cancer, and results in statistically significant improvements in survival, as well as in quality of life. However, the response rate to single-agent docetaxel is approximately 40% to 45%, emphasizing a need for alternative approaches. More significantly, with the onset of early, PSA-based detection of prostate cancer and closer follow-up, many men present with metastatic disease that remains asymptomatic. For such patients, the side effects of chemotherapy would compromise their current performance status and, thus, a nontoxic, early treatment option that could improve overall survival would be highly desirable. Immunotherapy represents one such approach; a number of clinical trials have suggested a survival benefit for immunotherapy in metastatic prostate cancer and confirmed that these agents are generally well-tolerated. As is the case for chemotherapy, it is doubtful that maximal survival benefit will be achieved with single-agent immunotherapy; experimental treatments in which mechanistically distinct immunotherapy approaches are combined, as well as approaches in which immunotherapy is combined with chemotherapy or hormonal therapy are currently under investigation. This review will discuss the mechanisms of action of several immunotherapy approaches for metastatic prostate cancer, focusing on active immunotherapy as opposed to administration of anti-tumor antibodies. The relative advantages and disadvantages of current approaches will be noted, and ongoing clinical trials will be highlighted.

Keywords

Immunotherapy; Vaccine; Antibody; Prostate; Lymphocyte; Dendritic cell; GM-CSF

Overview of an anti-tumor immune response

Over the past decade, the dendritic cell has emerged as the cell type of primary importance in the initiation and direction of an immune response [1]. Dendritic cells reside within the lymph nodes; in the immature state they sample their environment through pinocytosis at an enviable rate, often processing up their equivalent cellular volume hourly. When a “danger” signal is encountered, these cells cease their sampling activity, and transform into mature cells capable of initiating an immune response. This maturation is accompanied by the display of “antigen” on the cell surface, in forms that can be recognized by specific CD4 and CD8 T cells. Both cell types recognize their target antigens in the context of major

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histocompatibility (MHC) molecules, thus they can only be activated by dendritic cells derived from a genetically compatible host. If a successful anti-tumor immune response is initiated, the CD8 T cells are the primary effector cells—once adequately activated, these cells can traffic widely throughout the body and mediate a lytic (killing) response when their targets are recognized. CD4 T cells, in contrast, do not directly mediate lysis or tumor cell death, but provide “help” to allow CD8 T cells to become fully activated. This “help” is provided in the form of locally secreted cytokines and is generally indispensable for adequate CD8 T cell function.

One aspect of this process, which deserves further elaboration, is the actual mechanism of T cell activation. For full activation, T cells require two signals [2]. The first signal (Signal one) is transmitted when the T cell receptor binds to the proper peptide antigen in the context of MHC. However, Signal one alone does not lead to full T cell activation, a second signal is required, this is usually provided by the engagement of a T cell surface molecule known as CD28. Activated, stimulatory dendritic cells up-regulate molecules that bind to CD28, such as B7-1 and B7-2, and provide the appropriate “costimulation” (Signal two) for full T cell activity. Under certain conditions, T cells up-regulated a molecule known as CTLA-4 [3], which binds to B7-1 and/or B7-2 and BLOCKS the costimulatory signal (Signal two) from transmission. This process is physiological, and probably was designed to prevent autoimmunity. However, the B7/CTLA-4 interaction has also been co-opted by tumors in their ongoing efforts to subvert immunological recognition, and there is evidence that tumor-bearing hosts have a significant population of anti-tumor T cells held “in check” by CTLA-4 [3]. This concept of “co-inhibition” provides the basis for a number of tumor immunotherapy strategies, which will be discussed below.

Dendritic-cell based immunotherapy

Based on the above discussion, it is reasonable to postulate that the administration of activated dendritic cells, loaded with tumor-antigens, might be an excellent methodology by which to initiate an anti-tumor immune response. Dendritic cells can be derived by culturing immature monocytes from either bone marrow or peripheral blood in the presence of appropriate cytokines. This process typically takes 4 to 7 days in vitro. One of the critical choices in engineering a dendritic-cell “vaccine” is the choice of target antigen. While some dendritic cell immunotherapy approaches utilize tumor cell lysates as an antigen source, the more typical approach is to choose a promising tumor or tissue specific antigen. Dendritic-cell immunotherapy approaches for prostate cancer have studied a variety of potential tumor antigens as targets, including PSMA, PAP, and PSCA [4]. The approach that has advanced the furthest from a clinical standpoint is based on prostatic acid phosphatase (PAP) as a target antigen. This choice was based on early data, which showed that immunization of rodents with PAP could induce an autoimmune prostatitis, suggesting that immune tolerance to this particular prostatic protein was not complete [5]. Because of the relatively long in-vitro culture times required to mature conventional dendritic cells, the Dendreon Corp. (Seattle, WA), has adopted an approach involving only a brief ex vivo culture. Patients undergo leukopheresis and, from this product, immature monocytes are isolated under aseptic conditions. These cells are then cultured ex vivo with a proprietary cassette containing the target antigen (PAP), as well as the coding sequence of the gene for human

granulocyte macrophage colony stimulating factor (GM-CSF). After a brief ex vivo culture, the patient's transfected cells are infused intravenously, where GM-CSF produced from the transfected monocytes most likely promotes both dendritic cell maturation and activation. This approach, is therefore a personalized one, each patient's immunotherapy product must be manufactured individually.

Three single-agent clinical trials employing this approach have been published in the context of prostate cancer. The first Phase I Trial was reported by Burch et al. and in addition to demonstrating the safety of this approach, and also showed that additional peptide-based vaccination did not appear to augment the immune response initiated by the dendritic cell product [6]. These data were rapidly followed by a Phase I/II trial reported by Small et al., which showed the induction of immune responses against the recombinant fusion protein which makes up the "cassette" [7]. However, the most significant data regarding this approach were published only recently; Small et al. reported a Phase III trial comparing ProVenge (sipuleucel-T) with placebo in meta-static hormone refractory prostate cancer patients [8]. While the primary endpoint of the trial (time to progression) was not met, the data did suggest a significant survival advantage. These survival data are reasonably impressive when viewed in the context of the study design, which included a 2:1 randomization in favor of active treatment, and also permitted progressors treated with placebo to crossover to a second, active immunotherapy protocol. These data possibly represent the first Phase III demonstration that immunotherapy can improve survival in patients with metastatic prostate cancer. Based on those data, and on a second Phase III trial (D9902A), which has not yet been published, the company has applied to FDA for licensure; the deadline for review of this application is May 15, 2007 (www.dendreon.com).

Like all interventions, the dendritic-cell approach has potential advantages as well as disadvantages. One significant potential advantage to this approach concerns the dendritic cell population resident in cancer patients; a large body of data indicates that these cells are deficient in both number and function [9]. By culturing a significant population of activated dendritic cells ex-vivo, it might be possible to directly overcome these deficits. A second advantage of this approach is its single-antigen target, which facilitates immune monitoring. The major disadvantage of any approach that involves ex vivo cell culture is complexity and the potential for processing difficulties, a particular concern when widespread distribution is anticipated. A second potential disadvantage of single-antigen immunotherapy approaches is the potential for antigen escape, as has been noted in several trials of single-antigen vaccination for melanoma [10]. In the case of PAP targeting for prostate cancer this concern is largely theoretical; however it might prove interesting to analyze lesions in treated patients who eventually progress after immunotherapy with ProVenge for the presence of PAP by immunohistochemistry.

Immunotherapy based on gene-modified tumor cells

A large number of vaccines for infectious disease involve the administration of native pathogens that have been either attenuated or killed by heat or acid. These concepts were applied to tumor immunotherapy with limited success. However, in the early 1980s a number of groups began to utilize rapidly evolving genetic engineering technology to test

whether the production of cytokines could transform attenuated tumor cells into “vaccines”. The critical experiment in this regard was most likely that of Dranoff et al. who showed that transduction of tumor cells with the cytokine GM-CSF could engineer a protective anti-tumor immune response in an animal model of melanoma [11]. These data were actually quite surprising at the time, as other cytokines such as interleukin-2 and interferon-gamma were undergoing early phase trials in cancer patients. The notion that GM-CSF transduction of tumor cells could represent anti-tumor immunotherapy was first explored in a Phase I trial in renal cell cancer, in which an autologous tumor immunotherapy product was engineered by transduction of patients’ tumor cells (harvested at surgery) with GM-CSF [12]. This trial showed the approach to be safe and impressive but short-lived responses were noted in a number of patients. However, it became clear that patients’ tumor cells were, in general, extremely variable in terms of viability and transduction efficiency. A subsequent trial in prostate cancer confirmed these observations, but emphasized the difficulty and variability in producing a cancer immunotherapy product from a patient’s autologous tumor [13]. An approach to overcome the difficulties involved in engineering an autologous “vaccine” is based on the observation that the immune system is not primed by antigen on tumor cells, rather these cells are phagocytosed and antigen is presented on professional antigen-presenting-cells from the host, i.e. dendritic cells. This concept led to the hypothesis that a cell-based immunotherapy product could be created by using allogeneic cell lines transduced to produce the appropriate stimulatory cytokine, i.e., GM-CSF. This approach has been applied to a number of tumor types including pancreatic cancer, breast cancer and lung cancer as well as prostate cancer [14–17].

For a prostate cancer product, two cell lines were chosen in order to provide a nonoverlapping source of potential tumor antigens [15]. LnCaP was derived from disease metastatic to a lymph node, and expresses a number of prostate epithelial antigens including PSMA and PSA. PC-3 is an androgen-refractory line derived from a bone metastasis and expresses several cancer-associated proteases. The first clinical trial involving this approach was published only recently; this Phase I/II trial enrolled 21 men with hormone-naïve, biochemically relapsed disease. The immunotherapy product was well tolerated, and novel antibodies reactive with the LnCaP and PC3 cell lines were detected, suggesting immunological activity [18]. Commercially, this approach has been developed by Cell Genesys Inc. (South San Francisco, CA), who completed two Phase II trials, reported in abstract form (Table 1 and [15]). These two trials both included patients with metastatic HRPC, and a potential survival advantage has been suggested [15]. These trials also served to identify a dose and schedule for a larger Phase III trial, which was initiated in 2004. This trial, VITAL-1, is a 1:1 randomized, unblinded study comparing immunotherapy with GVAX prostate to standard chemotherapy with docetaxel in men with asymptomatic, hormone-refractory prostate cancer. The primary endpoint of this study is overall survival, and 600 men will be enrolled worldwide.

As is the case for dendritic-cell based therapies, the GVAX cell-based immunotherapy approach has potential advantages and disadvantages. The primary advantage of such an approach is the incorporation of multiple tumor and tissue antigens, which should provide broad applicability and perhaps minimize the potential for antigen escape. Another advantage to this approach lies in the manufacturing approach, which relies on standard cell-

culture technology. The disadvantages of a transduced cell-based approach to immunotherapy revolve around the diverse antigen profile presented—immune monitoring is technically and intellectually challenging. In addition, each target antigen in the product is probably present in relatively low concentration, explaining the biweekly treatment schedule determined by Phase II trials.

Immunotherapy based on viral vectors

Vaccination against viral pathogens dates back to 1796, when Edward Jenner showed that material from pustular lesions of individuals infected with cowpox could protect against future infection with variola (smallpox). The robust immune response engendered by pox-family viruses has been studied extensively in the context of tumor immunology in general, and prostate cancer in particular. The first Phase I trial of this approach was reported by Sanda et al., who administered a recombinant vaccinia virus encoding PSA (ProstVac) to men with biochemically relapsed prostate cancer [19]. These data were followed soon after by additional studies involving dose escalation of this agent, and which included more extensive immunological monitoring [20,21]. Early on it was realized that vaccinia-based vaccination would be limited by an antibody-mediated response against the vector itself, and clinical trials demonstrated a reduced potency of sequential doses [20]. In response to this obstacle, sequential addition of a second, replication deficient pox-virus based vector (fowlpox) targeting PSA was explored. A multi-center ECOG trial determined the optimal scheduling of vaccinia-PSA and fowl-pox-PSA vectors, and showed vaccinia priming followed by fowlpox boosting resulted in an optimal immune response [22]. This trial also suggested an improvement in progression-free-survival in treated patients. Further work with this approach involved the inclusion of three separate costimulatory molecules (LFA-1, ICAM, and B7-1), in an effort to further improve T cell immune responses [23]. In the case of metastatic HPRC, a randomized Phase II trial has been completed, and preliminary results were presented in abstract format by Kantoff et al. [21] (Table 1).

As is the case for the two technologies described above, viral-based immunotherapy approaches have both advantages and disadvantages. These agents are prepared with standard cell-culture techniques, allowing relatively straightforward manufacture of large quantities of material. In addition, the inclusion of a single primary antigen (PSA) facilitates immune monitoring. However, the genome of pox-viruses is relatively large, and a number of these transcripts may serve to down-modulate an immune response in vivo [24,25]. In addition, there have been some laboratory (but not clinical) data suggesting that vaccination with pox-virus based vectors can expand regulatory T cells (Treg) that down-modulate and immune response [26], but these studies have not been extended to the refined prime-boost, co-stimulatory scheme under study in current clinical trials.

Immune checkpoint blockade

Recent data in spontaneous animal models of cancer shows that a population of anti-tumor CD8 (Killer) T cells is expanded in vivo as tumors emerge and progress [27]. A number of host-specific and tumor-specific mechanisms restrain these specific CD8 T cells from performing their designated lytic function, including expression of the co-inhibitory T cell molecule CTLA-4. This molecule, originally described by Allison et al., plays a key role in

keeping immune responses in check: mice in which CTLA-4 has been genetically knocked out show a severe “autoimmune” phenotype and expire before 20 weeks of age [3]. A fully human monoclonal antibody against this molecule has been developed by the Medarex Corp. (Princeton, NJ), and tested in patients with renal cell cancer, melanoma, and prostate cancer [28]. It should be noted that clinical studies in prostate cancer were initiated after the completion of several studies in other tumor types. As might be inferred by animal studies, effective blockade of CTLA-4 results in auto-immune “breakthrough” events in a significant proportion of patients under study [29]. These events may range from a mild rash to severe colitis and hypophysitis. Meaningful clinical responses have been reported as well, and clinical response seems to correlate to some degree with the demonstration of autoimmunity. In prostate cancer, two trials of MDX-010 have been reported in abstract form (see Table 1). In both of these trials, autoimmune breakthrough events were noted, as well as clinical responses primarily in the form of changes in PSA slope and/or velocity. This approach has been further extended to a multi-site trial involving repeated administration of this agent in a dose-escalation paradigm (Table 2).

The relative advantage of immunotherapy approaches involving immune checkpoint blockade is that “vaccination” may not be necessary; release of T cells held in check by inhibitory mechanisms may release pre-primed responses. Unfortunately, in at least some patients, a significant population of self-specific T cells may be held at bay by identical mechanisms, suggesting that with these approaches it may be difficult to segregate anti-tumor immunity from auto-immunity. Thus, the overall clinical utility of approaches employing immune checkpoint blockade may be determined by the severity and duration of side-effects, as well as by the ability to adequately manage them in the clinical arena. From an immunological standpoint, however, these approaches have at the very least provided dramatic clinical evidence that cancer patients can mount clinically and radiographically significant anti-tumor responses.

Combination immunotherapy

With the relevant exception of docetaxel for metastatic prostate cancer, very few chemotherapy agents are used alone in the treatment of patients with metastatic disease. Thus, it seems likely that approaches combining immunotherapy with other treatment modalities, or perhaps even combining multiple immunotherapy agents, might prove useful in treating men with prostate cancer, particularly in the metastatic setting. This concept is not novel, in fact the NIH group has explored combination immunotherapy for prostate cancer, studying ProstVac with radiotherapy [30], secondary androgen-manipulation [31], and chemotherapy [32]. In general, these studies have been encouraging, documenting improved rates of PSA response (versus single-agent treatment), as well as increased rates of correlative immune responses. Combination with docetaxel is particularly interesting in this regard, preclinical data from a number of laboratories clearly show that administration of docetaxel prior to immunotherapy with cell-based immunotherapy leads to improved clinical outcome, without an unexpected increase in toxicity [33]. A Phase III clinical trial testing of this approach was initiated in 2005: VITAL-2 will compare q 3 weeks docetaxel to the same regimen with GVAX® immunotherapy in patients with symptomatic, metastatic HRPC. The

trial design mirrors VITAL-1, with a primary endpoint of survival, a 1:1 randomization scheme, and an accrual goal of 600 patients worldwide (Table 3).

In addition to the studies discussed above, it should also be noted that some of the earliest clinical trials in prostate cancer were combinatorial studies; the Phase I study of ProstVac reported by Sanda et al. tested this agent in the context of androgen-ablation. Strong experimental support for such an approach was provided initially by Mercader et al. who showed that activated CD8 T cells infiltrated the prostate glands of men who received neo-adjuvant androgen-ablation prior to radical prostatectomy [34]. Our group has extended these data using an autochthonous animal model of prostate cancer, showing restoration of vaccine response to a prostate-restricted antigen after androgen-ablation [35]. The Mayo group led by Dr. Eugene Kwon is currently examining this approach in a randomized Phase II trial designed to test whether addition of the immune checkpoint blocking agent MDX010 to brief (3 months) androgen-ablation will improve the frequency and duration of PSA responses in men with locally advanced disease. A related trial, testing the combination of androgen-ablation and GVAX immunotherapy in men with biochemically relapsed disease is currently in the planning stages at the Eastern Cooperative Oncology Group (ECOG).

Perhaps one of the most innovative combinatorial concepts for metastatic prostate cancer is the notion of combining multiple immunotherapy modalities. Indeed, a number of the studies involving ProstVac have incorporated systemic administration of GM-CSF, and Dr. Eric Small is currently examining the combination of checkpoint blockade (MDX010) and GM-CSF in a Phase I trial currently enrolling patients at UCSF (Table 3). From a mechanistic standpoint, it might also make sense to provide a positive stimulus to the immune system in the form of active immunotherapy, while at the same time mitigating the negative effects of co-inhibitory checkpoints. In a crude automotive analogy, this might correspond to applying the gas while at the same time taking one’s foot off the brakes. Preliminary results from such an approach were presented at the ASCO national meeting in 2006; Gerritsen et al. [36] showed that men with metastatic HRPC treated with a combination of GVAX immunotherapy for prostate cancer and MDX010 displayed both PSA and radiological responses, along with a measurable incidence of autoimmune breakthrough events. A Phase I trial currently enrolling patients at the NCI will further explore this approach by combining the Prost-Vac vaccine vector(s) with MDX010 and systemic GM-CSF.

Summary

Although at least three distinct immunotherapy approaches for prostate cancer have advanced to late-phase clinical trials, it seems unlikely that monotherapy with any of these agents will produce long-term remissions in a majority of prostate cancer patients with metastatic disease. Yet, these approaches are generally well-tolerated and lack the systemic side-effects typically associated with conventional chemotherapy. Thus, rational treatment approaches will either employ these agents early on, before the onset of symptoms in the time period when quality of life issues are paramount or, conversely, later on in the disease process in combination treatment strategies. The most innovative immunological approaches

to metastatic prostate cancer combine multiple immunotherapy strategies and are only beginning extensive clinical evaluation.

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Table 1

Completed single-agent trials of immunotherapy for prostate cancer[a]

Agent	Phase	Target population	No. patients	Comments	References[a]
ProVenge	I	Metastatic HRPC	13	Included dose escalation of subcutaneous peptide in addition to I.V. D.C. immunotherapy	[6]
ProVenge	I/II	HRPC with or without metastatic disease	31	12 patients in Phase I portion, 19 in Phase II	[7]
ProVenge	III	Metastatic HRPC, PAP positive	127	D9901: First Phase III trial of active immunotherapy in prostate cancer to report a significant survival benefit	[8]
ProVenge	III	Metastatic HRPC, PAP positive	98	D9902A: Companion Phase III trial with similar design to above	www.dendreon.com
GVAX Prostate	I	Unexpected metastatic disease at radical prostatectomy	8	Immunotherapy with transduced autologous cancer cells	[13]
GVAX Prostate	I/II	Biochemical relapse post-prostatectomy	21	First trial of allogeneic cell-based approach in prostate cancer	[18]
GVAX Prostate	II	Metastatic HRPC	34	Expanded version of above	2006 ASCO Prostate CA Symposium. Small E, et al. Abstract no. 254
GVAX Prostate	II	Asymptomatic, metastatic HRPC	80	Dose escalation	2006 ASCO Prostate CA Symposium. Small E, et al. Abstract no. 254
ProstVac	I	Biochemical relapse post-prostatectomy	6	First publication of vaccinia-based immunotherapy for prostate cancer, administered in context of androgen-ablation	[19]
ProstVac	I	Biochemical relapse post radical prostatectomy or radiation therapy, metastatic disease allowed	33	Includes dose escalation	[21]
ProstVac	I	Metastatic HRPC	42	Included dose escalation	[20]
ProstVac	I	Biochemical relapse	64	Determined optimal sequencing of vaccinia, fowlpox vectors	[22]
ProstVac VF	I	HRPC with or without metastatic disease	10	Phase I study of heterologous prime-boost strategy including TRICOM® in the metastatic setting	[23]
ProstVac VF	II	Metastatic HRPC	120	Randomized, double-blind, vector-controlled multi-site trial with PFS primary endpoint	2006 ASCO Annual Mtg. Kantoff P, et al, Abstract no. 2501
Ipilimumab	I	Metastatic HRPC	14	Single dose of MDX-010 at 3.0 mg/kg	2002 ASCO Annual Mtg. Davis TA, et al. Abstract no. 74
Ipilimumab	I/II	HRPC	45	4 doses MDX-010 (3.0 mg/kg) ± single “priming” dose of docetaxel	2006 ASCO Annual Mtg. Small E, et al. Abstract no. 4609

[a]Abstracted references are available online at www.asco.org.

Table 2

Ongoing single-agent trials[a]

Agent	Phase	Target population	No. patients	Comments
ProVenge® (sipuleucel-T)	IIII	Metastatic HRPC	500	IMPACT (immunotherapy in metastatic prostate adenocarcinoma treatment), 2:1 randomized, double-blinded trial comparing ProVenge I.V. q 2 weeks × 3 to empty vector. Primary endpoint is overall survival. Crossover to a second-line active treatment protocol is allowed for the control group upon progression.
GVAX® prostate	III	Progressive, metastatic HRPC, asymptomatic	600	VITAL-1 (vaccine immunotherapy with allogeneic prostate cancer cell Lines), 1:1 randomized, unblinded trial comparing first line immunotherapy (GVAX q 2 weeks × 13) to standard chemotherapy (docetaxel q 3 weeks × 9). Primary endpoint is overall survival.
Ipilimumab (MDX-010)	I/II	Metastatic HRPC, no chronic narcotic pain medication, prior chemotherapy allowed	34	Open-label, multi-site dose-escalation study of MDX-010 q 3 weeks × 4 doses.

[a]Current data available at www.clinicaltrials.gov.

Table 3

Selected ongoing combinatorial trials of immunotherapy for prostate cancer[a]

Agents	Phase	Target population	No. patients	Comments
GVAX® prostate 6 docetaxel	IIII	Metastatic, symptomatic HRPC	600	Randomized Phase III trial of combination therapy, primary endpoint = survival
GVAX® prostate + Ipilimumab	I	Metastatic HRPC	12 + 15	Phase I dose escalation trial combining Ipilimumab with GVAX® prostate. 12 patients in dose escalation phase, 15 patients at MTD
Prostvac® VF + Ipilimumab	I	Metastatic HRPC	24	Phase I trial combination trial based on the vaccinia-PSA-TRICOM approach, dose escalation of Ipilimumab, 3–6 patients/dose.
Ipilimumab + short-term androgen-ablation	II	Newly diagnosed PC, no prior chemotherapy, hormonal therapy or radiation therapy	108	Randomized trial comparing progression-free-survival in men treated either with 3 months of androgen-ablation, or the same combined with a single dose of Ipilimumab (MDX-010). Secondary endpoints include PSA response.
Ipilimumab + systemic GM-CSF	I	Metastatic HRPC	12–24	Combined dose-escalated Ipilimumab (MDX-010) with GM-CSF given for 14 out of 28 days.

[a]Current data available at www.clinicaltrials.gov.