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Current Perspectives in Prostate Cancer Vaccines

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Abstract

The use of vaccines as a potential therapeutic modality for the treatment of cancer has been extensively studied. Recent advances include identification and characterization of tumor-associated antigens, novel vaccine delivery systems, and the combination of vaccines with immune stimulants and other therapeutic modalities. Immunotherapy as a modality for treatment of prostate cancer has received significant attention. There are several characteristics of prostate cancer that make it an ideal target for immunotherapy. Prostate cancer's relative indolence allows sufficient time to generate immune responses, which may take weeks or months to mount. In addition, prostate cancer-associated antigens direct the immune response to prostate cancer cells, thus sparing normal vital tissue. This review focuses on promising new vaccines and novel perspectives in the treatment of prostate cancer.

Keywords

Prostate cancer; immunotherapy; vaccine; cancer vaccine; clinical protocols; tumor-associated antigens

INTRODUCTION

Prostate cancer, the second leading cause of cancer death among men in the United States [1], is an attractive model for cancer vaccine research. It is generally considered a slow-growing tumor, which may allow adequate time for a vaccine to activate the immune system [2]. In general, tumor-associated antigens (TAAs) are ideal targets for immunotherapy because they are specific to the cancer and are not expressed, or are minimally expressed, in normal tissue and essential organs. Prostate TAAs are mainly tissue-lineage antigens such as prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), and prostatic acid phosphatase (PAP). Since the prostate is not an essential organ, targeting prostate TAAs generally does not cause significant morbidity and is not associated with significant systemic side effects [3, 4]. Another advantage of prostate cancer as a model for immunotherapy is the use of PSA for early detection of recurrent disease. This allows for the initiation of vaccine immunotherapy while tumor burden is still minimal [5]. Finally, since there are few cytotoxic therapies of proven benefit for advanced prostate cancer, this patient population is unlikely to be immunocompromised due to multiple rounds of cytotoxic treatments.

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IMMUNE ENHANCEMENT

Because cancer can develop and progress in the presence of an intact immune system, TAAs are by definition weakly immunogenic. Cancer vaccines are designed to increase the immunogenicity of TAAs and break immune tolerance. Strong antigen presentation by antigen-presenting cells (APCs) is required to sufficiently activate cytotoxic T cells (CTLs). Dendritic cells (DCs) are the most potent APCs and are key elements in T-cell activation. APCs internalize the antigen, process it, and express it on their surface as a peptide bound to major histocompatibility complex (MHC). T cells only recognize the TAA peptide-MHC complex on the surface of APCs; they do not recognize the antigen as a protein. Thus, activating APCs that are able to properly process and present the antigen is pivotal to adoptive immune system activation. T cells are activated in a dual-signal process. The first signal binds the peptide-MHC complex on the surface of the APC to the T-cell receptor (TCR) on the surface of the T cell. The second signal involves the interaction of T-cell costimulatory molecules on the surface of the APC with their corresponding ligands on the surface of the T cell, which leads to T-cell proliferation. A weak first or second signal can produce suboptimal T-cell activation and ineffective immune response [6].

Several T-cell costimulatory molecules have been identified, including B7.1 (CD80), lymphocyte function-associated antigen (LFA)-3, and intercellular adhesion molecule (ICAM)-1 [7, 8]. Genes from these costimulatory molecules have been engineered into vaccine vectors such as poxviruses, resulting in improved antigen-specific T-cell response [9].

Strategies to enhance DC and CTL activation and function have employed various cytokines. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is frequently used as an adjuvant to vaccine therapy [7]. GM-CSF injected at the vaccination site has been shown to induce the growth and maturation of DCs and to increase their infiltration to regional lymph nodes [8, 10], while enhancing antigen-specific T-cell responses and delayed-type hypersensitivity reactions [7]. Transduction of GM-CSF genes into whole tumor cells has shown similar effects. Another cytokine known to affect T-cell function is interleukin (IL)-2, which has antitumor activity as a single agent in melanoma and renal cell carcinoma and as an adjuvant to peptide vaccines for melanoma [11, 12]. Metronomic-dose IL-2 as an adjuvant to vaccine therapy has produced immune responses similar to standard-dose IL-2, with a much better safety profile [13]. Other cytokines with antitumor and immunogenic activity, such as IL-7, IL-12, and IL-15, are currently under investigation [14–16].

PROSTATE CANCER VACCINES

1. Dendritic cell vaccines

DCs play a crucial role in the activation of naïve CD4 and CD8 T cells, and thus bridge the innate to adoptive immune response. Researchers in cancer immunotherapy have focused a tremendous amount of interest in DC physiology, activation, maturation, and antigen presentation. In an effort to enhance their function, DCs have been loaded with peptides, proteins, and tumor lysates, infected with viral vectors, TAAs, and mRNAs or fused with tumor cells [17, 18]. However, the disadvantage of autologous DC-based vaccines is that their production is costly and labor-intensive. Large amounts of peripheral blood mononuclear cells must be cultured in the presence of several cytokines before being engineered and reintroduced into patients.

Sipuleucel-T (Provenge®; Dendreon, Inc.) is an autologous DC-based vaccine pulsed *ex vivo* with PA2024, a recombinant fusion protein of human PAP and GM-CSF. Two phase II

trials of sipuleucel-T in patients with CRPC showed a > 25% decline in PSA in 30% and 15% of patients, respectively. Immune responses correlated with improved time to progression [19, 20]. Subsequently, 2 phase III placebo-controlled studies were conducted in patients with metastatic CRPC, with a primary endpoint of time to progression. Both studies allowed for cross-over upon progression. The first trial did not meet its primary goal of prolonging progression-free survival, but there was a trend toward improved time to progression in patients receiving sipuleucel-T (11.7 vs. 10.0 weeks; $P = 0.052$). The trial, however, demonstrated an overall survival benefit favoring the treatment arm (median survival 25.9 months vs. 21.4 months; $P = 0.01$). Additional overall survival benefit was observed on longer follow-up. A total of 34% of patients in the sipuleucel-T arm and 11% in the placebo arm were alive at 36 months ($P = 0.005$). In the placebo arm, 34 patients (75.5%) crossed over to the sipuleucel-T arm. However, 36 months was not prespecified as the primary efficacy endpoint and results should therefore be interpreted cautiously. Based on the trial's failure to meet its primary endpoint, the FDA declined to approve sipuleucel-T and called for further study. A second study was also terminated early after the first study failed to meet its primary endpoint. A third phase III study called the IMPACT (Immunotherapy Prostate AdenoCarcinoma Treatment) trial was designed to have a primary endpoint of overall survival [21–23]. The results were recently presented at the 2009 American Urologic Association Annual meeting in Chicago, IL. The results of the intent-to-treat analysis demonstrated that sipuleucel-T extended median survival by 4.1 months compared to placebo (25.8 months vs. 21.7 months) and improved 3-year survival by 38% compared to placebo (31.7% vs. 23.0%). The IMPACT study achieved a P -value of 0.032, successfully exceeding the prespecified level of statistical significance defined by the study's design (P -value < 0.043), and sipuleucel-T reduced the risk of death by 22.5% compared to placebo ($HR = 0.775$). Furthermore, sipuleucel-T exhibited a favorable safety profile consistent with prior trials [24].

2. Vector-based vaccines

Vectors such as viruses, bacteria, or yeasts are a convenient vehicle for vaccine delivery. The advantages of using vectors are that (a) their large genomes allow for insertion of multiple genes for TAAs, costimulatory molecules, and cytokines; (b) some vectors cause an inflammatory response at the injection site, instigating migration of APCs to the site; (c) many vectors can infect the APCs, allowing for better antigen processing; and (d) compared to DC-based and autologous whole tumor cell vaccines, vector-based vaccines are easy and inexpensive to produce. The major disadvantage of some vectors is that host-induced humoral response can neutralize the vector and limit its efficacy with repeated use.

Poxviruses have been extensively studied as potential vaccine vectors. Vaccinia virus, used as a vector in many vaccines, induces strong immunostimulation at the injection site. Its large genome can integrate many transducible genes, and it has an excellent safety profile. Vaccinia has been administered to more than a billion people since the World Health Organization's 1967 launch of the Global Smallpox Eradication Program [25]. There was an initial concern that vaccinia-immune individuals would not be able to mount as strong an immune response as vaccinia-naïve individuals. Further investigation demonstrated that with higher doses of recombinant vaccinia viruses, even vaccinia-immune patients can generate a potent immune response. However, it has been shown that after 1 or 2 injections of vaccinia, immune response declines due to the effect of neutralizing antibodies. This has led to the development of a diversified prime-and-boost strategy, whereby the immune system is primed by replication-competent vaccinia virus, then boosted with a replication-defective avipox virus such as fowlpox, which is not associated with significant neutralizing antibodies [26–28]. Replication-defective vectors have the advantage of superior safety,

since they cannot replicate in the human body. They can, however, infect human cells and express their encoded transgenes for 2 to 3 weeks before cell death.

Poxviruses have been employed as vehicles for prostate cancer vaccines in various combinations. In a randomized phase II study in nonmetastatic CRPC, 42 patients were randomized to second-line hormonal therapy with nilutamide (an androgen receptor antagonist) vs. vaccine. The priming vaccine consisted of recombinant vaccinia (rV)-PSA and rV-B7.1, followed by monthly boosts of recombinant fowlpox (rF)-PSA. Patients on both arms were permitted to cross over to the other arm at PSA progression if their disease had not metastasized. Time to treatment failure was similar in both arms (9.9 vs. 7.6 months) [29]. The study showed an additional survival benefit in the 12 patients who received vaccine first followed by nilutamide, compared to those who received nilutamide first followed by vaccine (median overall survival 6.2 years vs. 3.7 years; $P = 0.045$) [30, 31].

PSA-TRICOM is a poxvirus-based vaccine expressing PSA plus 3 costimulatory molecules (B7.1, ICAM-1, and LFA-3). A phase I study in patients with metastatic CRPC demonstrated that a recombinant poxviral vaccine targeting PSA and containing TRICOM was well tolerated. Furthermore, evaluable patients treated with PSA-TRICOM in the phase I study had increases in PSA-specific T cells, and 9 of 15 patients had decreases in PSA velocity after vaccination [32].

Two phase II studies have demonstrated the clinical potential of PSA-TRICOM in patients with metastatic CRPC. In an industry-sponsored phase II trial, 125 patients with metastatic CRPC and Gleason scores of ≥ 7 were randomized to receive either PSA-TRICOM or wild-type vector control. Patients treated with vaccine were given a priming dose of rV-PSA-TRICOM and monthly boosts of rF-PSA-TRICOM. Patients in the control group were given monthly subcutaneous injections of fowlpox which, as an empty vector, induced no focused immune response. The study's primary endpoint was time to disease progression, as determined by new or significantly enlarging lesions observed on routine imaging. Although the study did not meet its primary endpoint, a survival advantage ultimately became apparent. Preliminary data showed that median overall survival was 24.4 months for patients treated with the vaccine, compared to 16.3 months for patients in the control arm. This suggests that, even though there was no benefit in terms of time to progression, there was a long-term benefit for patients treated with PSA-TRICOM. A final analysis confirmed this survival advantage, demonstrating an 8.5-month increase in overall survival among patients treated with PSA-TRICOM over patients treated with control vector ($P = 0.006$).^{1,2} A second phase II study in patients with metastatic CRPC evaluated 32 patients treated with PSA-TRICOM on a prime-and-boost schedule. Thirty-eight percent of patients experienced a PSA decline from baseline; median overall survival for all patients was 26.6 months, which exceeded the Halabi predicted survival of 17.4 months. For patients with more favorable prognostic factors (Halabi median predicted overall survival of 20.9 months), median overall survival has not been reached at 37.3 months.³

¹Kantoff, P.; Glode, L.; Tannenbaum, S.; Bilhartz, D. Randomized, double-blind, vector-controlled study of targeted immunotherapy in patients with hormone-refractory prostate cancer [abstract]. *J Clin Oncol*, **2005**, *24*(18S), 2501.

²Kantoff, P.; Schuetz, T.; Blumenstein, B.; Glode, M.; Bilhartz, D.; Gulley, J.; Schlom, J.; Laus, R.; Godfrey, W. Overall survival (OS) analysis of a phase II randomized controlled trial (RCT) of a poxviral-based PSA targeted immunotherapy in metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*, **2009**, *27*(15S), 5013.

³Madan, R.; Gulley, J.; Dahut, W.; Tsang, K.; Steinberg, S.; Schlom, J.; Arlen, P. Overall survival (OS) analysis of a phase II study using a pox viral-based vaccine, PSA-TRICOM, in the treatment of metastatic, castrate-resistant prostate cancer (mCRPC): implications for clinical trial design [abstract]. *J Clin Oncol*, **2008**, *16*(20S), 3005.

3. Autologous whole tumor cell vaccines

Autologous whole tumor cell vaccines are derived from the patient's own tumor cells in a time-consuming process that requires a significant amount of tumor tissue. The advantage of autologous whole tumor cell vaccines is that they target the patient's own TAAs and preclude the need for antigen preselection. One disadvantage, however, is that the antigens could be diluted by other cellular components. Other disadvantages include the lack of standardization measures and the difficulty of evaluating antigen-specific immune responses. In a phase I clinical study, 8 immunocompetent prostate cancer patients were treated with autologous, GM-CSF-secreting, irradiated tumor vaccines prepared from *ex vivo* retroviral transduction of surgically harvested cells. Expansion of primary cultures of autologous vaccine cells successfully met trial specifications in 8 of 11 cases; however, yields of the primary culture cell limited the number of courses of vaccination [33]. Other disadvantages include the lack of standardization measures and the difficulty of evaluating antigen-specific immune responses.

4. Allogeneic whole tumor cell vaccines

Allogeneic whole tumor cell vaccines are derived from various tumor cell lines and are easier to prepare. Whole tumor cells are rendered replication-defective by radiation and are frequently combined with nonspecific immunostimulants [34, 35]. GVAX (Cell Genesys, Inc.) consists of 2 prostate cancer cell lines, LNCaP and PC-3, transfected with a human GM-CSF gene. In a randomized phase II study of 55 chemotherapy-naïve patients with castrate-resistant prostate cancer (CRPC), 34 patients had radiographic evidence of metastasis and 21 patients had rising PSA only [8]. Patients were randomized to receive a priming dose of 500 million cells of GVAX and 12 boosts of either 100 million cells (low-dose GVAX) or 300 million cells (high-dose GVAX) biweekly for 6 months. Median survival was 26.2 months for the metastatic group and 37.5 months for the nonmetastatic group, more than 6 months longer than the median survival predicted for each group by the Halabi nomogram [36]. Patients with metastatic disease who received high-dose GVAX lived longer than those who received the lower dose (34.9 months vs. 24 months) [8].

A phase I/II dose escalation trial was conducted to confirm the above results and to determine the optimal dose of GVAX for phase III studies. The study included 80 patients with asymptomatic, chemotherapy-naïve, metastatic CRPC assigned to high-dose, intermediate-dose, and low-dose groups. The maximum tolerated dose was not identified. Median survival was 35, 20, and 23.1 months in the high-dose, intermediate-dose, and low-dose groups, respectively, compared to predicted survival based on the Halabi nomogram of 22, 20, and 18 months for the high-dose, intermediate-dose, and low-dose groups, respectively. Although, survival was greater in the high-dose group, PSA responses did not differ among the 3 groups [37].

Cell Genesys launched 2 phase III trials of GVAX. VITAL-1 was a multicenter, randomized, controlled phase III trial designed to compare GVAX to the standard of care (docetaxel plus prednisone) in asymptomatic metastatic prostate cancer patients. The primary endpoint of VITAL-1 was overall survival. VITAL-2 was a 2-arm randomized phase III study of GVAX in symptomatic metastatic prostate cancer patients. One arm combined GVAX with docetaxel and the other arm employed docetaxel and prednisone. VITAL-2 opened in May 2005 and was halted on August 27, 2008 because of increased deaths in the GVAX combination arm vs. the control arm (67 vs. 47) [38]. VITAL-1 completed recruitment of 626 patients in July 2007. Recently presented data suggest that the overall survival of asymptomatic, metastatic CRPC patients treated with GVAX was similar to those patients treated with docetaxel in VITAL-1 (HR 1.01). Of note, however, in the subgroup of patients with a Halabi nomogram predicted survival of > 18 months, there was a

trend toward improved survival in patients randomized to treatment with vaccine compared to patients treated with docetaxel (HR 0.9).^{4,5}

5. Peptide-based vaccines

L-BLP25 is a cancer vaccine that targets the exposed core peptide of MUC1 TAA. L-BLP25 is a lyophilized preparation consisting of a 25 amino acid peptide, immunoadjuvant monophosphoryl lipid A and 3 lipids, forming a liposomal product. In a small phase II study of L-BLP25, 16 patients who had 3 consecutive rises in PSA values $\geq 50\%$ over nadir following radical prostatectomy were enrolled and received 8 weekly vaccines [39]. Half of the patients demonstrated MUC1-specific proliferative T-cell responses and 6 patients had a post-vaccine PSA doubling time that increased by $> 50\%$ compared to baseline. Further trials with this vaccine are planned in prostate cancer.

CURRENT CONCEPTS IN PROSTATE CANCER VACCINE THERAPY

1. Combination therapy

Studies suggest synergistic effects with the combination of immunotherapy and conventional treatments for prostate cancer such as radiation, androgen-deprivation therapy (ADT), and certain chemotherapies. Radiation can alter tumor-cell phenotype and upregulate the expression of some TAAs, costimulatory molecules, and cytokine receptors. MHC class I and Fas are among the genes that can be upregulated by radiation [40–43]. A randomized phase II trial evaluated immune responses in patients undergoing definitive radiotherapy for prostate cancer. Thirty patients were randomized to receive radiation alone or in combination with a poxviral-PSA vaccine. Thirteen of 17 patients in the combination arm who received all 8 scheduled vaccinations had a 3-fold increase in PSA-specific T cells, compared to no increase in the radiotherapy-only arm ($P < 0.0005$) [44].

ADT has been shown to potentiate immune responses and mitigate immune tolerance to prostate cancer antigens [29, 30, 45]. Preclinical studies have shown that castration in aged male mice can cause regeneration of the thymus, with normalization of the thymic microenvironment and MHC class II expression in thymocytes increased to young adult levels by 4 weeks postcastration [46]. In one clinical study, T-cell infiltration of the prostate was observed after 1 to 3 weeks of ADT. These T cells were predominantly CD4+ and demonstrated an oligoclonal pattern of TCR restriction [47]. Another study showed an increase in tumor-associated autoantibody responses in patients receiving neoadjuvant ADT for prostate cancer [48]. A study in patients with androgen-dependent prostate cancer and rising PSA after prostatectomy randomized patients to sipuleucel-T or placebo following 3 months of ADT. There was a trend toward prolonged time to biochemical failure favoring the treatment arm.⁶ An ongoing randomized study at the NCI is examining whether there is a clinical benefit to combining antiandrogen therapy (flutamide) with vaccine (PSA-TRICOM) compared to antiandrogen therapy alone.

There are increasing data suggesting that the long-held belief that chemotherapy will blunt the ability of a vaccine to activate an immune response may not be completely accurate.

⁴Higano, C.; Saad, F.; Somer, B.; Curti, B.; Petrylak, D.; Drake, C.; Schnell, F.; Redfern, C.; Schrijvers, D.; Sacks, N. A phase III trial of GVAX immunotherapy for prostate cancer versus docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer (CRPC) [abstract]. *ASCO Genitourinary Cancers Symposium*, 2009, LBA150.

⁵Small, E.; Demkow, T.; Gerritsen, W.; Rolland, F.; Hoskin, P.; Smith, D.; Parker, C.; Chondros, D.; Ma, J.; Hege, K. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC) [abstract]. *ASCO Genitourinary Cancers Symposium*, 2009, 7.

⁶Beer, T.; Bernstein, G.; Corman, J.; Glode, L.; Hall, S.; Poll, W.; Schellhammer, P.; Xu, Y.; Yu, L.; Frohlich, M. Randomized trial of active cellular immunotherapy with sipuleucel-T in androgen dependent prostate cancer (ADPC) [abstract]. *J Clin Oncol*, 2007, 25(18S), 5059.

Certain chemotherapy agents have been shown to positively modulate the immune response through different mechanisms such as upregulation of TAAs and MHC class I, depletion of regulatory T cells, and increased cytokine production [49, 50]. A randomized phase II study of patients with metastatic CRPC compared docetaxel vs. a poxviral-PSA vaccine and demonstrated no difference in PSA-specific T-cell response [51]. However, it should be noted that in patients heavily pretreated with chemotherapy, the immune system could be impaired, so that combining chemotherapy with vaccine in these patients may not produce a potent immune response. Moreover, careful selection of the chemotherapy agent and close attention to vaccine/chemotherapy scheduling and dosing are critical considerations.

Monoclonal antibodies have been combined with vaccines for the treatment of various tumor types. In prostate cancer, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibody has been tested in combination with vaccines. CTLA-4 is a T-cell surface glycoprotein that is upregulated following T-cell activation to inhibit the immune response. Its main function is to prevent autoimmunity by regulating the body's immune activity. T cells express 2 counteracting receptors on their cell surface—CD28 and CTLA-4. Both bind to the same ligands or costimulatory molecules on the surface of APCs (B7.1 and B7.2, also known as CD80 and CD86). Binding of these costimulatory molecules to CD28 activates T cells, while interacting with CTLA-4 inhibits T-cell stimulation. Blocking CTLA-4 with a neutralizing antibody has been shown to sustain and potentiate immune responses [52–55]. A phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, and GVAX in 16 patients with metastatic prostate cancer suggested a correlation between immune-related adverse events and immune response.⁷ Another phase I trial, which recently closed to accrual, combined ipilimumab and PSA-TRICOM vaccine in metastatic prostate cancer patients. Clinical benefits included declines in PSA in 14 of 30 patients and increased PSA doubling time. From an immunologic standpoint, 5 of 9 evaluable patients had 2.5- to 5-fold increases in PSA-specific T cells.⁸

2. Clinical considerations

In the treatment of cancer, it is becoming more evident that traditional response criteria, which focus strictly on reduction of tumor size, may not be the best criteria for determining the efficacy of vaccine therapy. Tumors treated with vaccines may grow initially before shrinking, or may stabilize or grow at a slower rate. Therefore, overall survival may be a better endpoint than disease-free survival for evaluating vaccines in clinical trials. Furthermore, clinical and preclinical data suggest that vaccines are more effective in patients with small tumor volume and less aggressive disease [21, 56]. There are several possible reasons for this: (a) activation of an immune response outpaces tumor growth, (b) in a large tumor, T-cell infiltration and penetrance is incomplete, (c) immunosuppression in patients heavily pretreated with cytotoxic chemotherapy and radiation impedes optimal immune stimulation, and (d) immunosuppressive cytokines produced by tumor cells and/or suppressive cells in the microenvironment of a large tumor further hinder immune response. Based on these considerations, vaccine therapies may lead to better outcomes in adjuvant settings than in metastatic settings, while tumor burden is still relatively low. As previously discussed, sipuleucel-T demonstrated an overall survival advantage without a significant benefit in time to progression [21, 24].

⁷Gerritsen, W.; van den Eertwegh, A.; de Gruijl, T.; van den Berg, H.; Scheper, R.; Sacks, N.; Lowy, I.; Stankevich, E.; Hege, K. Expanded phase I combination trial of GVAX immunotherapy for prostate cancer and ipilimumab in patients with metastatic hormone-refractory prostate cancer (mHPRC) [abstract]. *J Clin Oncol*, **2008**, *26*, 5146.

⁸Mohebtash, M.; Madan, R.; Arlen, P. Phase I trial of targeted therapy with PSA-TRICOM vaccine and ipilimumab in patients with metastatic castration-resistant prostate cancer [abstract]. *ASCO Genitourinary Cancers Symposium*, **2009**, 184.

3. Immunologic concepts

Better understanding of APCs and the mechanisms of T-cell activation have led to the development of a new generation of vaccines that incorporate costimulatory molecules. One finding on the physiology of adoptive cell-mediated immune response is that T-cell quality and avidity are more important than quantity. Use of costimulatory molecules and cytokine adjuvants can increase the function and cytolytic activity of T cells [50, 57].

Another advancement in our understanding of the mechanism of immune response regulation is the identification of regulatory T cells (Tregs). A subtype of CD4⁺ T cells, Tregs are responsible for downregulating host immune activation, thereby reducing the risk of autoimmunity. Tregs may play an important role in immune tolerance and anergy to TAAs; higher levels of Tregs correlate with negative clinical outcomes in some cancers [58, 59]. Types of regulatory cells include CD4⁺CD25^{high}FoxP3⁺ Tregs, immature macrophages, and CD4⁺NKT⁺ cells [60, 61]. Ongoing research is focusing on ways to inhibit these cells and thus increase the efficacy of tumor vaccines. Low-dose cyclophosphamide has been shown to deplete Tregs without affecting CTLs [62–65]. Monoclonal antibodies targeting CD25, an IL-2 receptor, have been used to target Tregs. Denileukin diftitox (OntakR; Ligand Pharmaceuticals, San Diego, CA), a fusion protein of IL-2 and diphtheria toxin, has been shown to inhibit Tregs in preclinical and clinical models [66, 67].

Another area under study is the phenomenon of “antigen cascade” or “epitope spreading.” This refers to an immune response to tumor antigens or antigen epitopes not incorporated into the vaccine [68]. Further characterization of antigen cascade may lead to recognition of new immunogenic targets for tumor vaccines.

CONCLUSION

Vaccine strategies for the treatment of prostate cancer are under active investigation, using a wide variety of approaches including whole tumor cell vaccines, DC approaches, and vector-driven delivery of TAAs. Preclinical and clinical results of studies employing these various vaccine approaches have demonstrated immunologic responses that, in some instances, correlate with clinical activity of these vaccines. Larger clinical studies are needed to validate these findings.

Novel vaccine strategies are also being implemented, including the addition of costimulatory molecules to help activate and proliferate T-cell responses, and combination therapies with cytokines, antibodies, hormones, and chemotherapy that may help reduce regulatory Tregs and initiate an antigen cascade that could allow additional tumor antigens to be targeted by the immune system.

Importantly, there now are several studies which have demonstrated clinically improved overall survival in patients with metastatic prostate cancer. Indeed, the definitive IMPACT study may well lead to the first FDA-approved therapeutic vaccine to be licensed for any cancer. These positive trials raise the hypothesis that vaccines have a greater impact on survival when used in patients with lower volume disease or less aggressive disease (i.e., those with longer predicted survivals). This suggests that immunotherapy may generate sustained downward pressure on the growth rate of the tumor for months to years after the vaccine, and that despite the lack of dramatic-but-transient decreases in tumor volume seen with cytotoxic therapies such as chemotherapy, this slowed growth rate can eventually lead to improved survival. This improvement in survival is more likely to be accentuated if a vaccine is started earlier in the disease process.

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