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Therapeutic Prostate Cancer Vaccines: A Review of the Latest Developments

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Abstract

Therapeutic cancer vaccines are well-tolerated immunotherapy modalities designed to activate the immune system to kill cancer cells without a significant effect on normal cells. Better understanding of tumor immunology has led to improved strategies in vaccine development, which have resulted in improved outcomes. This review discusses different types of cancer vaccines, focusing predominantly on prostate cancer vaccines because of the high prevalence of prostate cancer and the wide variety of approaches used in prostate cancer immunotherapy.

Keywords

Carcinoma; prostate cancer; vaccines; prostate-specific antigen; clinical trials; poxviral vectors

Introduction

Current strategies in cancer vaccine development include a variety of approaches, broadly categorized as cell-based, vector-based, and protein/peptide-based vaccines. Many potential targets for cancer immunotherapy have been identified, including the tumor-associated antigens (TAAs) carcinoembryonic antigen, MUC-1, HER-2/*neu*, and prostate-specific antigen (PSA). T cells are critically important in the immune response against TAAs. In particular, the role of $CD8^+$ cytotoxic T lymphocytes in tumor regression has made them a major focus in the development of anticancer vaccines. It is important to note that the activated T cells induced by vaccination do not recognize the surface proteins or shed proteins of target antigens—only the peptide-major histocompatibility complex (peptide-MHC) complex of the TAA on the cell surface. Thus, targets of vaccine therapy need not be cell-surface proteins. In the past decade, identification of numerous TAAs, combined with immunostimulatory strategies, has led to the development of highly targeted vaccines for cancer immunotherapy.

Prostate cancer is the most common noncutaneous cancer and the second leading cause of cancer death among men in the United States. Prostate cancer is an ideal model for vaccine development since it is generally an indolent disease. Also, PSA allows for early detection of recurrent disease when tumor burden is still small. Finally, there are few therapeutic options for patients with recurrent disease following definitive therapy with surgery or radiation. This review discusses new developments in therapeutic cancer vaccines in general, with a particular focus on prostate cancer vaccines. Table I summarizes the

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application of some of these approaches in recently conducted prostate cancer clinical studies.

Whole Tumor-Cell Vaccines

Whole tumor-cell vaccines can be autologous, where the patient's own tumor cells are used in the vaccine, or allogeneic, where various tumor cell lines are employed. Development of autologous whole tumor-cell vaccines is labor-intensive and requires a significant amount of tissue. However, because they contain the patient's specific TAAs [1], tumor antigens do not need to be preselected, and there is a greater chance that an autologous whole tumor-cell vaccine will contain unidentified immunogenic antigens. However, standardization of autologous whole tumor-cell vaccines is complicated, thus making measurement of vaccine-specific immune responses more difficult, and the TAAs in the vaccine may be diluted by normal cellular components of the tumor [2, 3]. Conversely, allogeneic whole tumor-cell vaccines, which are made from various tumor cell lines, are faster and easier to prepare [4].

Whole tumor-cell vaccines are made replication-defective by irradiation. They are frequently coadministered with nonspecific adjuvants such as bacillus Calmette-Guerin (BCG). New technologies are currently available to enhance the immunogenicity of vaccines, *i.e., ex vivo* manipulation of tumor cells to produce cytokines including interleukin (IL)-2, IL-4, tumor necrosis factor (TNF)-alpha, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [5].

GVAX (Cell Genesys, Inc.) is a whole tumor-cell vaccine used in prostate cancer. It consists of 2 allogeneic prostate cancer cell lines genetically modified to produce GM-CSF. Two phase II single-arm, multicenter trials in metastatic castration-resistant prostate cancer (CRPC) patients showed a median survival of 26.2 to 35.0 months [4, 6]. Based on these data, there are currently 2 ongoing phase III trials evaluating GVAX with or without chemotherapy in prostate cancer patients, with the primary endpoint of overall survival (OS).

Allogeneic whole tumor-cell vaccines modified to secrete GM-CSF have also been employed in patients with pancreatic cancer. A 60-patient phase II study in the adjuvant setting showed that post-chemotherapy induction of mesothelin-specific $CD8^+$ T cells correlated with progression-free survival [7]. The median OS of 26 months compared favorably with chemotherapy alone in this same patient population at the same institution.

Onyvax-P (Onyvax Ltd.) is another whole tumor-cell vaccine consisting of 3 irradiated allogeneic prostate cancer cell lines. The first 2 injections of Onyvax-P are given with BCG. A phase II study of Onyvax-P in nonmetastatic CRPC patients showed a significant decrease in PSA doubling time, which correlated with immune responses [8, 9]. The median time to progression was 28 weeks and compared favorably to other trials in this setting [10]. However, given the heterogeneity seen in this patient population, only a randomized placebo-controlled study can determine the efficacy of this strategy. Such a trial recently completed enrollment in Europe. Another randomized vaccine vs. placebo study in prostate cancer patients with biochemical recurrence after definitive therapy is underway at the National Cancer Institute (NCI) [11].

“Dendritic Cell” Vaccines

Dendritic cells (DCs), the most potent antigen-presenting cells (APCs), can activate naïve $CD4^+$ and $CD8^+$ T lymphocytes by presenting antigens on their surface in conjunction with MHC class I and II molecules. DCs, which are immature in most tissues, have an exceptional ability to capture and process antigens. This, in turn, signals the cells to mature and mobilize to regional lymph nodes. Different antigen-loading procedures have been used

to produce *ex vivo* DC-based vaccines, where a patient's DCs are pulsed by synthetic HLA-binding peptides, tumor lysates, messenger RNA (mRNA), or TAA/cytokine gene transfer by a viral vector. The disadvantage of DC-based vaccines is that developing them is costly and labor-intensive. Leukapheresis is required to collect mononuclear cells, which are subsequently cultured for several days in the presence of cytokines before being reinfused into the patient [12]. Another challenge is sustained antigen presentation. Transduction through recombinant viruses, including adenoviruses and retroviruses, is highly effective. However, viral gene expression may occur, which may prime antiviral immunity, including cytotoxic T-cell lysis, leading to rapid lysis of DCs in subsequent rounds of immunization. New vectors such as gutless adenoviruses that do not express viral gene products, or fowlpox vectors that do not express “late” viral gene products, may overcome this obstacle [13]. DC vaccine development is still an area of great interest in cancer immunology and many trials are underway to evaluate their efficacy.

Sipuleucel-T (Provenge; Dendreon, Inc.) is made from an autologous APC-enriched product plus a fusion protein consisting of prostatic acid phosphatase and GM-CSF. The combined results of 2 placebo-controlled randomized phase III trials in patients with metastatic CRPC have shown a statistically significant increase in 36-month OS (33% vs. 15%; hazard ratio, 1.5; $P = 0.011$) in patients treated with sipuleucel-T (n =147) vs. placebo (n = 78). However, the primary endpoint of progression-free survival did not reach statistical significance in either of these trials [4, 5]. An OS endpoint study has completed accrual and initial results are expected in late 2008.

Another approach being employed in the clinic is the use of fusion cell vaccines that combine DCs with autologous tumor cells for immunotherapy of patients with breast and renal cell cancer. A phase I clinical trial conducted in this population demonstrated this type of vaccine's ability to induce both immunologic and clinical responses [14].

Other approaches to DC vaccines in prostate cancer include mRNA-pulsed DCs, autologous DCs pulsed with recombinant PSA (Dendritophage-rPSA), and allogeneic tumor lysate-pulsed DCs. All of the phase I/II trials employing such vaccines have shown promise, but further evaluation is needed to confirm the vaccines’ clinical utility.

Vector-Based Vaccines

Tumor-antigen DNA sequences can be transferred to a variety of viral vectors that are either replication-competent or replication-incompetent in mammalian cells. Commonly used replication-incompetent viral vectors include modified vaccinia Ankara, fowlpox, or canarypox. There are also recombinant viral vectors, specifically mutated and rendered self-replication incompetent, such as adenovirus, retrovirus, and lentivirus. One advantage of recombinant poxviruses is their capacity to carry multiple transgenes, enabling them to express not only TAAs but also various costimulatory molecules. Costimulation is essential for a potent immune response, especially in the context of weak antigens such as TAAs. Selected vector-based vaccines are also able to infect APCs, allowing them to process the antigens. Another advantage of vector-based vaccines is that, compared to other types of cancer vaccines, they are relatively inexpensive to prepare.

Diversified vaccine prime-and-boost strategies using replication-competent vaccinia vector (rV-PSA) as prime followed by replication-incompetent fowlpox vector (rF-PSA) as boost have produced provocative results. In a phase II study of 64 patients with rising PSA after definitive local therapy, patients were randomized to receive 4 vaccinations with recombinant vaccinia-PSA (designated V) and/or recombinant fowlpox-PSA (designated A for avipox) in various sequences. Patients in the VAAA arm showed a substantial increase in progression-free survival over patients in the AAAV or AAAA arms [15]. In a phase II trial

at the NCI, patients with nonmetastatic CRPC were randomized to receive either a recombinant vaccine (rV- expressing PSA admixed with rV- expressing the B7.1 costimulatory molecule, followed by booster vaccine of rF-PSA) or hormone therapy with nilutamide. Patients on either arm who developed rising PSA without metastasis could cross over to receive both vaccine and nilutamide. In both crossover groups, OS was evaluated from the date of crossover. The 12 patients treated with vaccine then nilutamide had a median OS of 4.8 years, compared to a median OS of 2.8 years for the 8 patients who received nilutamide then vaccine ($P = 0.028$) [16].

Other phase I and phase II studies have employed this prime-and-boost strategy in patients with metastatic CRPC. Patients received a priming vaccine composed of vaccinia-PSA plus the costimulatory molecules B7.1, ICAM-1, and LFA-3 (designated TRICOM), followed by monthly fowlpox-PSA/TRICOM boosts. This strategy was well-tolerated, and patients were able to mount PSA-specific T-cell responses against PSA [17]. An additional 32 patients were enrolled on the phase II study. Median OS for 17 patients with a predicted OS of 22 months was significantly prolonged at 37 months; 38% of patients showed a decline in PSA. Furthermore, a > 6-fold increase in T-cell response correlated with an increase in OS. Five patients who had a ≥ 6-fold increase in PSA-specific T-cell response remain alive at 35 to 45+ months after enrollment, compared to a median OS of 20.3 months in patients with a < 6-fold increase in PSA-specific T-cell response ($P = 0.038$). These findings suggest that the clinical benefit of the vaccine may be more pronounced in patients with more favorable prognostic indicators [18].

Peptide-Based Vaccines

Peptide-based vaccines contain peptide antigens with the appropriate HLA-restricted amino acid sequence. Peptides alone are usually weakly immunogenic and need to be structurally modified or given with an immunologic adjuvant. Many tumor-antigen epitopes have low binding affinity for MHC molecules, usually due to a lack of optimal amino acids at the peptide-binding sites. Substitution of amino acids at anchor sites enhances the binding capacity of tumor peptides. Peptide-based vaccines require HLA typing and matching for each patient in order to provide the appropriate peptide epitope. However, more recent approaches have utilized complex multipeptide mixtures that contain more than one HLA allele, thus increasing the percentage of patients who would be eligible for this therapeutic modality [19].

Peptide vaccines have been combined with various adjuvants, as well as with cytokines such as IL-12 and GM-CSF. The cost of producing peptide vaccines is relatively low. Peptide vaccines were first studied in patients with metastatic melanoma and have since been studied in cancers of the pancreas, breast, ovary, cervix, liver, lung, and prostate. In studies carried out with the HER-2/*neu* peptides with or without GM-CSF, patients with breast cancer were able to generate HER-2-specific immune responses [20]. Recent studies evaluating E75, an immunogenic HLA-A2-restricted peptide derived from the HER-2/*neu* protein, have demonstrated this vaccine's activity in patients with breast cancer [21, 22]. E75 has also been safely tested in a phase I trial of prostate cancer patients with a high risk of recurrence [23]. A phase II trial of the vaccine with or without GM-CSF is underway in prostate cancer patients.

Conclusions

As our understanding of the field of tumor immunology has expanded, novel vaccines and vaccine strategies have been developed. The advantage of using whole tumor-cell vaccines is that several tumor antigens, some of which have yet to be defined, may be present in the vaccine. However, this approach has major disadvantages as well. The amount of a

particular antigen in the vaccine may be diluted by normal cellular components of the tumor. DCs express an exceptionally high number of the MHC, costimulatory, and adhesion molecules needed for sufficient T-cell activation. However, isolating and manufacturing DCs is both costly and time-consuming. Immunization with live recombinant poxvirus vectors allows for the expression of foreign antigens encoded by a transgene directly into various cells of the host, including professional APCs. This method enables antigen processing and presentation of antigenic peptides, along with host histocompatibility antigens and other necessary cofactors found on the APCs. Newer strategies utilizing peptides for immunotherapy of a variety of cancers have also shown promise. All of the various approaches discussed here have been employed in numerous clinical trials, and current studies are now employing vaccines in combination with standard-of-care therapies and other experimental agents.

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Table 1

Overview of several clinical trials of prostate cancer vaccine immunotherapy.

Ref.	Patient population	Study design	Vaccine regimen	Pts (n)	Median OS/% PSAV decline
3	Metastatic CRPC	Phase III	APC/PAP/GM-CSF	82	25.9 mos
			Placebo	45	21.4 mos
4	Metastatic CRPC	Phase II	GVAX:		
			High-dose	22	35 mos
			Mid/low-dose	25/33	20/23 mos
2	Metastatic CRPC	Phase II, randomized	PSA/TRICOM	84	24.4 mos
			Vector control	41	16.3 mos
2	Metastatic CRPC		APC/PAP/GM-CSF, then docetaxel	51	50% at 36 mos
			Control, then docetaxel	31	25% at 36 mos
17	Nonmetastatic CRPC	Phase II, randomized	V Π nilutamide	12	6.2 yrs
			Nilutamide Π V	8	3.7 yrs*
6	D0 PC	Phase I/II	GVAX	21	↓PSA velocity: 76%

APC: antigen-presenting cell; CRPC: castrate-resistant prostate cancer; GM-CSF: granulocyte-macrophage colony-stimulating factor; OS: overall survival; PAP: prostatic acid phosphatase; PSA: prostate-specific antigen; V: rV-PSA/B7.1, rF-PSA vaccine.

*$P = 0.045\%$