There has been a resurgence of interest in developing noncytotoxic immune therapies for patients with either hormone-naïve biochemically relapsed post-primary therapy or castrate metastatic prostate cancer. The rationale for developing an immunotherapeutic approach has been based on the overexpression and underglycosylation of a wide variety of altered "self" molecules including prostate-specific antigen (PSA), acid phosphatase (ACP), prostate stem cell antigen (PSCA), and prostate-specific membrane antigen (PSMA), which can serve as targets for immune recognition and attack. In addition, such a strategy could theoretically make use of the patient's immune system to fight the tumor particularly if their disease is of reasonably low volume. A variety of immunotherapeutic approaches have been explored through phase I, II, and now phase III trials demonstrating that immunologic tolerance could be broken, as evidenced by the development of high-titer antibodies and T-cell responses specific for the tumor. What appears to be revolutionizing the immunotherapy field is the combination of vaccines with cytokines or immune modulators, which not only potentiate immune reactivity in vivo but foster dramatic antitumor responses. This review explores the challenges now faced in establishing a role for immune therapies for prostate cancer treatment.

Although the use of docetaxel (Taxotere) improved survival in men with hormone-refractory prostate cancer, the benefits of other therapeutic modalities that have been seen in other malignancies have evaded prostate cancer research. Although not usually considered the prototypical malignancy that interacts with the immune system (such as melanoma and renal cell carcinoma), prostate cancer does have some "attributes" that make it a candidate for such an approach: well identified antigenic targets, an indolent behavior in some patients, and a tumor marker that allows the detection of disease recurrence or progression at a minimal tumor volume.

**Challenges and Accomplishments**

Dr. Slovin's article comprehensively outlines the challenges and accomplishments in the arena of prostate cancer immunotherapy. The development of monoclonal antibodies with therapeutic efficacy against prostate cancer has not yet reached the level of activity seen in other solid tumors. One reason for this delay is the lack of cell-surface molecules that serve as immunologic targets and are readily expressed and accessible to antibody. Unlike prostate-specific membrane antigen (PSMA), prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are not membrane-bound, and so, despite their broad presence on prostate cancer cells, are not suitable targets for antibody therapy.

J591 is a humanized monoclonal antibody against PSMA that has been linked to yttrium-90 or lutetium-177. In phase I trials, hematologic toxicity was dose-limiting, but some patients received multiple doses; phase II studies are planned.[1-2] MLN2704 is an immunoconjugate that uses J591 to deliver DM1, a maytansinoid antimicrotubule agent, directly to prostate cancer cells. A phase I/II study involving 21 patients showed preliminary activity with a greater than 50% PSA decline in three patients and 25%-50% PSA decline in four patients.[3] Toxicities included neuropathy, fatigue, nausea, and anorexia. These results are promising in showing some indirect measure of antitumor activity, but further work is needed to improve responses and minimize toxicity.

**Dendritic Cell Vaccines**

Dendritic cell vaccines attempt to more effectively promote antigen presentation by a variety of approaches: fusion with a tumor cell, pulsing (with a protein, peptide, antibody, or apoptotic tumor cells), or transfecting with a viral vector. The feasibility and clinical activity of sipuleucel-T-autologous antigen-presenting cells cultured ex vivo with a fusion protein, PA2024 (PAP linked to granulocyte-macro-phage colony-stimulating factor [GM-CSF])—was demonstrated in a randomized phase III trial showing improvements in T-cell response and median survival compared with placebo.[4] Another vaccine, DCVax-Prostate, also uses autologous dendritic cells but pulsed ex vivo with peptides against PSMA. Responses were seen in 19 of 95 men treated in a phase II trial, but ProstaScint scans were used to determine responses, so results must be interpreted with caution.[5]
A variation of this approach used allogeneic tumor lysate to pulse the dendritic cells and was demonstrated to be safe with PSA-specific T-cell responses in a phase I trial.[6]

**Other Vaccines**

Dendritic cell vaccines are at a disadvantage due to the cost and effort required for their preparation. Other vaccines use prostate cancer cells or peptides to stimulate an immune response. The spectrum of these vaccines ranges widely, depending on the use of autologous or allogeneic cell lines, viral vectors, and immunomodulators. GVAX is a whole-cell vaccine that uses irradiated, allogeneic prostate cancer cells modified to secrete GM-CSF. This vaccine is now being evaluated in a phase III study comparing GVAX with docetaxel/prednisone.

Onyxvax Ltd uses three allogeneic prostate cancer cell lines administered in conjunction with heat-killed *Mycobacterium vaccae* as an adjuvant. Despite positive results in immunologic parameters, no clinical responses have been seen.[7] A similar vaccine also uses three allogeneic cell lines given with bacillus Calmette-Gurin (BCG) as an adjuvant. In this study, 11 of 26 patients showed prolonged decreases in PSA velocity.[8]

Other vaccines use acellular approaches, primarily through viral vectors (poxvirus) to initiate antigen presentation using peptides in conjunction with immunologic adjuvants. Several of these vaccines have been in clinical trials in different patient populations ranging from newly diagnosed to metastatic hormone-refractory states. Researchers at the National Cancer Institute have studied a poxvirus vaccine transfected to express PSA and the costimulatory molecule B7.1 in patients undergoing radiation therapy for localized disease. The rationale for this approach is that radiation can induce the expression of cell-surface markers that can make the tumor cells more susceptible to immune-mediated cell death.

Preclinical studies have shown that the taxane paclitaxel can enhance the antitumor response of vaccines, and at least one study has shown that docetaxel can be administered concurrently without affecting the vaccine-specific T-cell responses.[9] Ongoing studies are combining chemotherapy with vaccines including GVAX with docetaxel. Newer vaccines, such as PSA-TRICOM, contain multiple costimulatory molecules (B7.1, ICAM-1, and LFA-3) and are currently under investigation.

**Further Considerations**

Immunotherapy for prostate cancer is feasible, but optimizing the immune response remains a priority. Host immune tolerance is perhaps the biggest challenge. Regulatory T cells appear to play a role in inhibiting the antitumor immune response in several cancers including prostate cancer. Prostate cancer patients have higher proportions of regulatory T cells both in the tumor tissue and in the peripheral blood (compared with normal donors). Studies are under way using MDX-010 (ipilimumab, an anti-CTLA-4 antibody) in combination with vaccines (GVAX, PSA-TRICOM) to "knock out" the regulatory T cells and allow a more robust immune response. Preliminary results of these studies have yielded some intriguing observations, including the occurrence of autoimmune disorders (such as autoimmune hypophysitis, thyroiditis, or adrenal insufficiency) at the time PSA responses were noted.

One of the most challenging aspects of tumor immunology involves elucidation of the tumor microenvironment. As Dr. Slovin correctly states, the demonstration of immune responses to any of these therapies does not automatically imply a clinical response. The observation of an immune response in the periphery does not equate with a response at the tumor site. The array of preclinical studies demonstrating the importance of the tumor microenvironment in the host antitumor response is too extensive to list in this commentary, but the evidence continues to mount that altering the tumor microenvironment (with cyclo-oxygenase [COX]-2 inhibitors, vascular endothelial growth factor [VEGF] inhibition, etc) may be a necessary step in overcoming immune tolerance. Hopefully, findings in the near future will provide us with additional insights that will translate into better results for our patients.

—Ralph Hauke, MD

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**References:**


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