Poxviral-based vaccine elicits immunologic responses in prostate cancer patients

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Prostvac is a poxviral-based vaccine designed to target prostate-specific antigen (PSA) in prostate cancer patients. Recently, the potential toxicity and immunological impact of this immunotherapy were reviewed in the context of new clinical data. Our findings suggest that Prostvac is safe and elicits anticancer immune responses, both alone and in combinatorial approaches.

Prostvac (PSA-TRICOM) is a poxviral-based therapeutic cancer vaccine designed to enhance antitumor immune responses in vivo.1 This treatment employs modified vaccinia (priming) and fowlpox (booster) vaccines. These viruses are genetically engineered to express prostate-specific antigen (PSA), the target antigen, with three T-cell co-stimulatory molecules (B7.1, ICAM-1, and LFA-3) in order to initiate immune responses. Multiple phase II trials of Prostvac, both alone and in combination with other agents, have suggested that this anticancer vaccine may provide clinical benefit. Prostvac is now entering phase III testing (NCT01322490) enrolling metastatic, castration-resistant prostate cancer (mCRPC) patients internationally, randomized according to Prostvac alone, Prostvac with GM-CSF (immune adjuvant) or wild-type fowlpox (as a control).2,3 We recently presented updated and new data from clinical trials testing Prostvac as a prostate cancer therapeutic vaccine, focusing on its safety and ability to elicit an immune response.4

First and foremost, these data reaffirmed the lack of toxicity associated with Prostvac. An analysis of 234 patients treated with over 1300 injections demonstrated a negligible side effect profile, with the most common ≥ grade 2 toxicity being injection-site reactions occurring after 21.6% of vaccinations. These self-limiting events were typically mild, with only 2 occurrences of grade 3 injection-site reactions. Additional adverse events, mostly flu-like symptoms, were seen after 1.5% (grade 2) and 0.5% (grade 3) of doses administered.

Immunologic assessments were performed on mCRPC patient samples derived from various clinical trials, including single-agent use, and in combination studies with radiotherapy (NCT00005916), antiandrogens (NCT00020254, NCT00450463), docetaxel (NCT00045227), and ipilimumab (NCT00113984).4 Of these 104 patients, 59 (57%) had a greater than 2-fold increase in PSA-specific T cells approximately 28 days after their first vaccine (see Table 1). The magnitude of the responses was similar to influenza-specific T cells, indicating a robust immune response to this self-antigen. Additional T-cell responses exceeding 2-fold increases were detected in response to 2 to 4 additional tumor antigens not found initially in the vaccine (i.e., antigen spreading) in 19/28 patients (68%).

Beyond T-cell activation, associations were also observed between clinical outcome and regulatory T cells (Treg). mCRPC patients treated with Prostvac alone had better survival outcomes if Treg function declined after vaccine administration (P = 0.0029) relative to patients without Treg declines. Similarly, increases in CD4+ effector T cells after vaccine correlated with longer survival. Furthermore, patients with improved ratios in effector T cell to CTLA-4+ Tregs after vaccine tended to live longer than estimated using a validated nomogram prediction algorithm for mCRPC patients. Interestingly, a separate study involving intraprostatic vaccination suggested that, after vaccination, there were declines in Tregs relative to CD4+ T cells.5

Additional mCRPC studies of Prostvac alone found no changes in the frequency of natural killer cells. There were also no global changes in cytokines consistent with a T helper type 1 (Th1)- or type 2 (Th2)-specific response. Also noteworthy, anti-PSA antibodies were detected in only 2/349 patients treated with poxviral-based vaccines targeting PSA. Furthermore, high correlations were seen between PSA and prostatic acid phosphatase (another circulating prostate cancer biomarker) prior to and after Prostvac (Spearman’s correlation r = 0.76 and 0.77, respectively). These PSA data collectively suggest that PSA biomarker kinetics are not artificially altered.

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by Prostvac-induced immune responses, and thus PSA-based metrics may be used to assess the benefits of Prostvac.

Our work provides proof of concept demonstrating the ability of Prostvac to generate an immune response, including 57% of patients who had PSA-specific responses.4 For several reasons addressed in this paper, this likely underestimates the true extent of the immune response. What these data do not support, however, is the use of these individual immunologic parameters as a surrogate biomarker for clinical benefit. In fact, some of the antigen-specific data would caution against it. The fact that 68% of treated prostate cancer patients evaluated had antigen responses to non-PSA antigens highlights the prospective potency of such anticancer immunologic stimulation, but also shows that, similar to prior observations in metastatic breast cancer trials, once initiated, “antigen spreading” following vaccine therapy can be broad and vary among patients.6 This personalized and dynamic immune response generated in vivo may allow the antitumor immune response to target the spectrum of phenotypically distinct tumor cells within a patient, but it makes it difficult and impractical to evaluate a patient’s immune response to every possible antigen. Therefore, the absence of a robust PSA-specific response may not preclude the possibility of clinical benefit. Additional data suggest that responses to secondary antigens may be more vital to the overall antitumor response.6,7

Alterations in the frequency of Tregs and Treg functional changes apparent after vaccination are provocative, as increased Treg function is associated with poor clinical outcomes in prostate cancer.8 Relative declines in Tregs after vaccination were generally associated with better outcomes, suggesting the vaccine was able to alter the immune cell balance, including relative declines in the occurrence of Tregs and Treg function, leading to improved outcomes. Further prospective analysis is required, but these hypothesis-generating data suggest that combination studies with agents that impair Tregs or in patients with low Tregs (minimal tumor burden) could potentiate better clinical outcomes with Prostvac.

The absence of PSA antibodies after Prostvac suggests the feasibility of studies evaluating PSA kinetics. Previous data suggest that while there may not be consistent short-term declines in PSA after Prostvac, there may be a slowing of PSA kinetics, ultimately resulting in long-term clinical benefit.9,10 Multiple trials are prospectively evaluating this hypothesis with Prostvac in both non-metastatic (NCT01875250) and metastatic prostate cancer (NCT01322490). Accumulating data suggest Prostvac’s immunologic impact, but the clinical experience will ultimately dictate its therapeutic role in prostate cancer. The phase III trial (NCT01322490) will evaluate survival in mCRPC, but other phase II trials are investigating combinations in early (NCT01875250) and advanced (NCT01867333) disease. Additional studies are planned or ongoing in the (neo) adjuvant setting (NCT02153918). These studies and future trials will attempt to translate the immunological data summarized here into meaningful improvements in cancer patient outcome in the clinic.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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