**Advances in Brief**

**A Phase I Trial of a Recombinant Vaccinia Virus Expressing Prostate-specific Antigen in Advanced Prostate Cancer**

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Abstract

A recombinant vaccinia virus encoding human prostate-specific antigen (rV-PSA) was administered as three consecutive monthly doses to 33 men with rising PSA levels after radical prostatectomy, radiation therapy, both, or metastatic disease at presentation. Dose levels were $2.65 \times 10^6$, $2.65 \times 10^7$, and $2.65 \times 10^8$ plaque forming units. Ten patients who received the highest dose also received 250 µg/m2 granulocyte-macrophage colony-stimulating factor (GM-CSF) as an immunostimulatory adjunct. No patient experienced any virus-related effects beyond grade I cutaneous toxicity. Pustule formation and/or erythema occurred after the first dose in all 27 men who received GM-CSF. GM-CSF administration was associated with fevers and myalgias of grade 2 or lower in 9 of 10 patients. PSA levels in 14 of 33 men treated with rV-PSA with or without GM-CSF were stable for at least 6 months after primary immunization. Nine patients remained stable for 11–25 months; six of these remain progression free with stable PSA levels. Immunological studies demonstrated a specific T-cell response to PSA-3, a 9-mer peptide derived from PSA. rV-PSA is safe and can elicit clinical and immune responses, and certain patients remain without evidence of clinical progression for up to 21 months or longer.

Introduction

Prostate cancer was diagnosed in ~174,500 men in 1998 (1). Thirty percent of patients have metastatic disease at presentation, and of those treated with primary radical prostatectomy or radiation therapy, a significant proportion will relapse. Treatment with androgen ablation for recurrent prostate cancer, although providing effective palliation in many patients, is rarely curative, and the vast majority patients eventually demonstrate progressive disease (2–4). Effective hormonal therapy requires surgical or medical castration with resulting impotence, loss of libido, loss of muscle mass, weight gain, gynecomastia, and hot flashes. Patients with rising PSA3 after primary therapy will inevitably progress to overt metastatic disease. At present, the treatment options for this group of patients with small tumor burdens and otherwise normal health are to wait for the occurrence of overt metastatic disease, to begin hormonal therapy with its attendant side effects, or to enroll in investigational therapies.

Because PSA is expressed exclusively in prostatic epithelial cells, whether normal or transformed, it represents an attractive target for immunotherapy (5). The availability of a recombinant vaccinia virus that expresses rV-PSA allows clinical testing of this concept. Because vaccinia evokes both humoral and cell-mediated responses, co-expression of PSA with viral proteins may enhance immunogenicity to cells expressing PSA, resulting in the lysis of cells expressing this antigen.

CTLs recognize protein antigens as small peptides (9–10 amino acids long) associated with MHC class I molecules (6, 7). Previous studies involved a determination of whether PSA contains epitopes capable of binding class I HLA A2 molecules and could elicit CD8+ cytolytic T-lymphocyte responses, and whether the CTLs generated could lyse human prostatic cancer cell lines in a MHC-restricted manner (8, 9). The HLA-A2 allele was chosen for study because it is expressed in ~50% of the population and the HLA binding motifs for peptides are known. Several peptides within the PSA molecule have been identified that bind the A2 site. These peptides, when incubated with PBMCs from normal donors (serving as antigen-presenting cells) in the presence of interleukin-2, were able to generate T-cell lines. Several of these T-cell lines when pulsed with one of these peptides, designated PSA-3, were able to lyse HLA-A2-positive target cell lines and cell lines infected with rV-PSA but not wild-type vaccinia-infected cells. More importantly, these T-cell lines were able to lyse human prostatic carcinoma cell lines and other cell types expressing PSA and possessing the HLA-A2 allele (8). Subsequent studies have identified other

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3. The abbreviations used are: PSA, prostate-specific antigen; rV-PSA, recombinant vaccinia virus expressing PSA; PBMC, peripheral blood mononuclear cell; pfu, plaque-forming unit(s); GM-CSF, granulocyte/macrophage-colony stimulating factor; CEA, carcinoembryonic antigen; DLT, dose-limiting toxicity; Flu, influenza.
epitopes of PSA capable of eliciting CTLs that will lyse PSA expressing prostate carcinoma cells (9).

Recombinant vaccinia virus constructs expressing tumor-associated antigens have been developed and tested in primates and humans with significant toxicity (10–12). In a preclinical toxicology study, rV-PSA was administered to rhesus monkeys, which have a 94% amino acid homology to human PSA. Local erythema, regional lymphadenopathy, and transient elevations of WBC counts were observed. Mild temperature elevations were seen in some animals. There was no effect on body weight, clinical chemistries, or other untoward effects. A PSA-specific IgM response was seen in all monkeys tested, and all four of the monkeys inoculated with 1 × 10^8 pfu rV-PSA developed specific T-cell responses to PSA protein for up to 270 days (13).

Several biological adjuvants have been used to enhance T-cell responses to tumor-associated antigens. One of the more promising of these adjuvants is recombinant GM-CSF (14–16). When administered either at the site of a peptide immunization in experimental systems or with an anti-idiotype monoclonal antibody protein in clinical studies, GM-CSF was shown to enhance antigen-specific immune responses (14, 15). In recent experimental studies, GM-CSF was shown to enhance the immune response to CEA when given the day of and 3 consecutive days after a rV-CEA vaccine (17).

We have conducted a phase I trial of rV-PSA vaccine in men with advanced cancer of the prostate. We report here that administration of rV-PSA is safe and that the vaccine induces PSA-specific immune responses and potential clinical activity.

Patients and Methods

Patient Selection

Patients were required to have a histologically confirmed diagnosis of prostatic adenocarcinoma and evidence of advanced disease by any of following: (a) lymph node involvement with cancer and PSA ≥ 10 ng/ml; (b) bone scan representing metastatic cancer and PSA ≥ 10 ng/ml; (c) post radical prostatectomy with rising PSA ≥ 2 ng/ml (three determinations monthly or greater); or (d) post radiation therapy and PSA ≥ 10 ng/ml and rising. Patients needed to be Eastern Cooperative Oncology Group performance status 0 or 1; have adequate hematological, hepatic, and renal function; have normal immunological testing as defined by positive delayed hypersensitivity skin testing (mumps, Candida, and trichophytn); have a CD4:CD8 ratio > 1; and have normal serum immunoglobulin levels. Prior vaccinia exposure (as the small pox vaccine in childhood or during military service) was required, either by documentation, presence of an inoculation scar, or patient history. Neoadjuvant hormonal therapy was permitted as long as the preceding criteria for prostate cancer progression were met.

Exclusion criteria were prior hormonal therapy or chemotherapy for advanced disease, a history of autoimmune diseases associated with altered immune function, and prior splenectomy or active cases of skin disorders, such as eczema, extensive psoriasis, disseminated zoster, burns, or impetigo. Evidence of metastatic bony disease, including bony pain or radionuclide imaging, was an exclusion.

Treatment Plan

rV-PSA vaccinations were administered to each patient at 4-week intervals for a total of three doses. Three dose levels were used. Six patients were treated at the lowest dose level and evaluated for toxicity at 4 weeks after initial vaccination before they were entered at the next higher dose level. Patients were followed weekly until 28 days after the final dose (day 85) and then monthly for 6 months. When the highest dose of the rV-PSA vaccine was reached, an additional five patients were treated to further assess potential toxicity. An additional 10 patients were treated with GM-CSF in conjunction with the rV-PSA at dose level of 2.65 × 10^8 pfu. GM-CSF (250 μg/m^2) was administered s.c. on days −1, 0, 1, and 2 of the rV-PSA treatment. The intradermal rV-PSA was administered in the skin immediately above the s.c. GM-CSF site. If patients experienced nonhematological toxicity of grade 3 or higher, the GM-CSF dose was reduced to 125 μg/m^2.

Patients were seen weekly for the first 2 months, and then monthly. Complete interval histories, physical examinations, blood chemistries, electrocardiograms, and serum PSA were obtained. All patients were evaluated for toxicity by the Common Toxicity Criteria 2.0 (http://www.ctep.nci.nih.gov) and the vaccinia toxicity grading scale (Centers for Disease Control). Patients were followed until disease progression.

DLT was defined as any of the following: grade 4 vaccinia toxicity; grade 4 hematological toxicity; or grade 3/4 nonhematological toxicity, except nausea, vomiting, or fever. The maximum tolerated dose was defined as the dose below that dose at which DLT occurred in two patients.

Vaccinia-related Toxicity Grading. Vaccinia-related toxicity grading was as follows: grade 1, cutaneous reaction extending ≤10 cm from the vaccination site; grade 2, generalized cutaneous reaction extending >10 cm from the vaccination site, and autoinoculation syndrome without sequelae; grade 3 was not applicable; grade 4, autoinoculation syndrome with sequelae; post vaccinia encephalitis, vaccinia gangrenosum, eczema gangrenosum, and Stevens-Johnson syndrome (18).

Criteria for Response. No patient on this trial had measurable disease. Therefore, the following response criteria were used: complete response was defined as normalization of the PSA value for three successive monthly determinations; a partial response was defined as a decline of PSA value by >80% (without normalization) for three successive monthly determinations; stable disease was defined as a decline in PSA of <80% or an increase in PSA value up to 50% for three successive monthly determinations; and progressive disease was defined as any increase in PSA to >50% above baseline for three successive monthly determinations or the appearance of new lesions.

Vaccine Formulation

rV-PSA, constructed and manufactured by Therion Biologicals Corporation, was provided by the NCI (NSC no. 678892). The vaccine was derived from the Wyeth [New York City Board of Health, associated with the lowest incidence of clinical complications (19)] strain of vaccinia by the insertion of the PSA gene into the viral genome (13). Two equivalent lots of rV-PSA were used during the study. The first lot included vials containing 0.1 ml of vaccine at a concentration of 2.65 × 10^9 pfu/ml in PBS with 10% glycerol. In the second lot, vaccine
vials contained 0.3 ml at a concentration of $1.17 \times 10^9$ pfu/ml. Administration was via intradermal inoculation using a needle and syringe. A sterile, nonadherent dressing (i.e., “Telfa”) was used to cover the site.

Collection of PBMCs

PBMCs were collected in heparinized tubes from HLA-A2-positive patients treated with rV-PSA and GM-CSF. The mononuclear cell fraction was separated by Ficoll-Hypaque density gradient separation, washed three times with cold PBS, and frozen in 90% heat-inactivated AB serum and 10% DMSO at $-80^\circ$C until assayed. Five vials per patient were stored, with $1 \times 10^7$ cells/vial. After collection of serial samples, each patient’s pretreatment, postvaccination-1, post-2, and post-3 serum, 2 mM glutamine, 0.1 mM nonessential amino acids, 1 mM sodium pyruvate, 50 μM β-mercaptoethanol, 100 units/ml penicillin, and 100 μg/ml streptomycin (20).

Immunoassay

PBMCs from pre, post-1, post-2, and post-3 immunizations were thawed and used as effector cells. PBMCs were seeded at a concentration of $2 \times 10^7$/well in six wells. Cells were cultured for 24 h in the presence of PSA-3-pulsed C1R-A2 cells (stimulator:effector ratio = 1:5) and measured at 490 nm using an ELISA microplate autoreader (Bio-Tek Instruments, Winooski, VT).

Table 1: Toxicity

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<th>Cardiovascular</th>
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<td>0/11</td>
<td>0/11</td>
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<td>0/10</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

* Grades 2 and 3.

After incubation overnight at room temperature, the wells were washed four times with assay buffer, and 50 μl of a 1:4000 dilution of peroxidase-conjugated goat antihuman IgG (Kirkgaard & Perry, Gaithersburg, MD) were added to each well. A 1:2000 dilution of peroxidase-conjugated goat antimurine IgG (Kirkgaard & Perry) was used for the PSA antibody control. After incubation at 37°C for 1 h, wells were washed four times with assay buffer, and 100 μl each of the chromogen O-phenylenediamine dihydrochloride (Sigma, St. Louis, MO) and hydrogen peroxide were added to each well. After a 10-min incubation in the dark, the reaction was stopped with 25 μl of 4N HNO3. The absorbance of each well was measured at 490 nm using an ELISA microplate autoradiometer. (Bio-Tek Instruments, Winooski, VT).

Results

Safety. Thirty-three men were treated over a 22-month period. The median age was 62 years (range, 47–74 years). No DLT occurred, and no maximum tolerated dose was reached due to the formulation potency of rV-PSA. At the highest dose, $2.65 \times 10^9$ pfu, treatment with $250 \mu g/m^2$ of GM-CSF was added.

The toxicities observed are shown in Table 1. No vaccinia-related toxicity higher than grade 1, a local reaction at the site of inoculation, occurred in any patient. There was no lymphadenopathy, hepatosplenomegaly, fever, malaise, or leukocytosis attributable to the recombinant vaccine. In the 10 patients treated with GM-CSF, 1 patient developed grade 3 fever and tachycardia after the first dose of GM-CSF, prior to rV-PSA administration, and required a dose reduction to $125 \mu g/m^2$. This dose was tolerated without further symptoms.

The cutaneous responsiveness to the first and subsequent rV-PSA vaccinations is listed in Table 2. Thirty-two of 33 patients responded locally to the first administration of rV-PSA. At doses $\geq 2.65 \times 10^7$ pfu, the majority of patients exhibited local responses even after the third vaccination (not all patients were assessed after the third inoculation for a cutaneous reaction).

Immune Responses to PSA. T-cell assays using the HLA-A2 class I allele 9-mer peptides PSA-3 and Flu matrix were used to investigate T-cell responses in patients positive for the HLA-A2 allele in the cohort of patients treated with $2.65 \times 10^9$ pfu rV-PSA plus GM-CSF. Seven patients were positive for the class I HLA-A2 allele. Ficoll-purified PBMCs from each of these patients were viably frozen at $1 \times 10^7$ cells/ml. PBMCs were obtained pre vaccination and 1 month after each vaccination for each patient. ELISPOT assays using the PSA-3 and Flu controls were also used as a positive internal control.
peptides were done simultaneously and coded. PBMCs were assayed after only 24 h in culture in the presence of peptide to rule out the effects of in vitro selection of T-cell populations. Results are expressed as a precursor frequency of IFN-γ-secreting cells in response to the given peptide.

As listed in Table 3, responses to the Flu peptide were similar pre vaccination and after each of three vaccinations with rV-PSA. These data served as an internal control for the ELISPOT assay using the PSA-3 peptide. Increases of at least 2-fold in precursors specific for PSA-3 peptide were observed in five of seven patients after three vaccinations, with patient 33 showing a >4.6-fold increase. In these five patients, the greatest increase in PSA-specific precursor frequency was observed after the first vaccination. Subsequent vaccinations did not produce substantial additional increases.

All 33 patients were tested for IgM and IgG antibodies to PSA. One patient (patient 24) developed low-level IgG antibodies to PSA. No other patient tested positive for anti-PSA antibodies (data not shown).

Clinical/Serum PSA Responses. Fig. 1 shows the number of months that each patient exhibited stable PSA levels after primary vaccination. PSA levels in 14 of 33 men treated with rV-PSA with or without GM-CSF were stable for at least 6 months after the initial immunization. Nine patients remained stable for 11–25 months. Six patients remain on study with stable PSA levels. Two patients had elevated lactate dehydrogenase levels at the time of initial enrollment, which remained elevated after vaccination. The progression-free interval for these patients ranged from 11 to 21 months. In addition to continuing to exhibit stable PSA levels, the six patients remaining on study showed no signs or symptoms of prostate cancer, including restaging bone scans.

Nineteen of 33 patients showed a decrease in PSA levels at some time during the treatment period. This transient decrease was not associated with detectable IgG antibody formation to PSA (data not shown). Several patients developed T-cell immune responses associated with prolonged stabilization.

**Discussion**

PSA is a 34-kDa glycoprotein produced by prostatic epithelial cells lining the glandular acini and ducts (1, 22). PSA is a serine protease of the glandular kallikrein gene family, which when secreted into prostatic and seminal fluid hydrolyzes seminal vesicle proteins important in semen liquefaction. Although present in the serum of healthy males at low levels, elevated PSA levels are correlated with prostatic epithelial growth, being elevated in 40% of men with benign prostatic hypertrophy. Men with prostate cancer show exponential increases in circulating levels of PSA (23). PSA is expressed in the majority of primary and metastatic prostate cancers, making it a target for cancer immunotherapy.

*In vitro* studies have demonstrated the generation of human CTLs specific for peptides derived from PSA (15). PSA-1 and

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<th>Dose 1</th>
<th>Dose 2</th>
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<td>10</td>
<td>2.65 × 10^6 pfu</td>
<td>10/10</td>
<td>10/10</td>
<td>7/10</td>
</tr>
</tbody>
</table>

* Not all patients assessed.

Table 2 Number of patients exhibiting cutaneous response* after each immunization.

Table 3 ELISPOT assay for IFN-γ production in PBMCs of patients pre- and post vaccinations with rV-PSA (plus GM-CSF).

Results are expressed as precursor frequency of IFN-γ-secreting cells. PBMCs from pre, post-1, post-2, and post-3 vaccinations were used as effector cells. PBMCs were seeded at a concentration of 2 × 10^6/well in six wells. Cells were cultured for 24 h in the presence of PSA-3-pulsed C1R-A2 cells. Flu matrix peptide 58-66 was used as control. A higher number of precursors is expressed as a smaller number in the denominator of the precursor frequency. Increases in precursor frequencies ≥2-fold were considered positive. Statistically significant difference (P = 0.0313, univariate procedure using the SAS system) for the following comparison: PSA-3 (pre vs. post). No statistically significant difference (P = 0.1000, univariate procedure using the SAS system) for comparison with Flu peptide 58-66 (pre vs. post).

<table>
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* Erythema >1 with or without vesicle formation.

\[ \text{GM-GSF} \]
PSA-3, peptides with HLA-A2 binding motifs of 10 amino acids in length, produced CTLs from the PBMCs of normal human donors capable of lysing HLA-A2-positive CIR-A2 cells pulsed with these peptides or HLA-matched prostatic carcinoma cell lines. Inoculation of human HLA-A2/Kb transgenic mice with a PSA peptide produced CTLs against PSA-expressing, HLA-A2-restricted cell lines. PSA-specific CTL clones demonstrated cytolytic activity against HLA-A2-positive CIR-A2 cell lines infected with rV-PSA but not against the same leukemic cell lines infected with wild-type vaccinia only, further demonstrating that human cells can process PSA so that PSA-peptide MHC complexes on cell surfaces make that cell susceptible to CTL-mediated lysis (16). PSA can be considered a potential target for cell-mediated immunotherapy. This would be particularly applicable in circumstances where prostate ablation by prostatectomy or radiotherapy has been performed and a rising PSA would be indicative of metastatic disease.

Vaccinia virus is a DNA orthopoxvirus with a large genome that serves well as an expression vector for large foreign proteins (24, 25). Unlike other DNA viruses, vaccinia replicates in the host cell cytoplasm. Under the regulation of a vaccinia promoter, the inserted foreign genes are transcribed and translated, and the resultant proteins are processed and transported (26). Inoculation of epidermal keratinocytes by scarification, intradermal, or s.c. routes produces a localized infection that allows expression of the foreign gene in host cells, and with virus multiplication, there is amplification of antigen with greater potential for immune reactivity. Both humoral and cell-mediated immunity can be elicited toward the foreign gene product (27, 28).

Preclinical safety trials in rhesus monkeys demonstrated that rV-PSA is safe and capable of inducing PSA-specific immune responses in a dose-dependent fashion. No evidence of autoimmunity or histopathology was observed. Three clinical trials using recombinant vaccinia vectors encoding CEA (rV-CEA) have demonstrated local vaccination site erythema, vesicular/pustular reactions, regional node swelling, malaise, and fevers without any other toxicity (6–8), as well as the generation of CEA-specific T-cell responses (13).

This phase I trial of rV-PSA demonstrated that repeated vaccination with rV-PSA is safe and nontoxic in men with prostate cancer. The addition of GM-CSF increased the incidence and severity of toxicity, but all of the toxicities were deemed a consequence of cytokine therapy and were mild in all but one circumstance. Cutaneous responses indicative of viral replication occurred in 32 of 33 patients despite previous exposure to vaccinia virus as a smallpox vaccine. Other than a local dermal reaction, there was no vaccinia-related toxicity.

Recombinant GM-CSF was used in these studies because previous preclinical and clinical studies using peptide or protein as immunogen showed that GM-CSF enhanced T-cell responses (14–16). In one of these studies in a rat model (14), the optimal dose and schedule was to administer GM-CSF at the injection site the day of vaccination. A recent study in a murine model not only confirmed that this dose schedule was optimal, but also demonstrated that it enhanced the CEA-specific T-cell responses when a recombinant vaccinia virus was used as immunogen (17). These studies also showed that GM-CSF enhanced the infiltration of dendritic cells to regional lymph nodes (17).

A recently reported limited phase I clinical trial evaluated the safety and biological effects of rV-PSA administered in six

![Figure 1](attachment:figure1.png)

*Fig. 1* Number of months that each patient exhibited stable PSA levels after primary vaccination. Stable PSA levels are defined as a decline of <80% or an increase in PSA levels up to 50%. + indicates that PSA levels remained stable in that patient.
patients with androgen-modulated recurrence of prostate cancer after radical prostatectomy. Toxicity was minimal, and DLT was not observed. Noteworthy variability in the time required for androgen restoration (after interruption of androgen deprivation therapy) was observed. Primary anti-PSA IgG antibody activity was induced after rV-PSA vaccination in one patient. One patient had a prolonged period with undetectable serum PSA levels after androgen restoration (29).

Seven HLA-A2 positive patients treated with 2.65 × 10^8 pfu rV-PSA and GM-CSF in our trial had PBMCs assayed for the development of a PSA peptide-specific T-cell immune response. Increases of at least 2-fold in precursors specific for the PSA-3 peptide were observed in five of seven patients after three vaccination, with one patient showing a 4.6-fold increase, whereas precursor frequencies specific for the control Flu peptide never increased more than 0.2-fold in any patient tested. In four of these five patients with an increased PSA-specific immune response, there was stabilization of serum PSA levels for 6–11+ months.

Stabilization of serum PSA has continued in 6 of 33 patients for 11+ to 21+ months. Several other patients were observed to have stabilization in the serum PSA levels for periods up to 2 years. The doubling time of the PSA for 6 months prior to vaccination with rV-PSA as opposed to that in 6-month intervals after vaccination suggests a change in the course of the disease in some patients. The PSA response correlated with the lack of any other marker of disease progression in these patients. The rise in PSA over time suggests that immunity needs boosting at periodic intervals.

The studies reported here demonstrated that rV-PSA vaccination enhanced T-cell responses to PSA after the first vaccination only, as opposed to the second or third. This is most likely due to host-immune responses to vaccinia proteins that limit the replication of the vaccinia virus. All of the patients in this study had received a small pox vaccination in childhood and most again during military service, thus enhancing the probability of a strong immune response to vaccinia proteins. These findings, along with preclinical observations (28), suggest that rV-PSA is best used in priming the immune system to a weak antigen such as PSA, and that another immunogen be used to boost the immune response.

These stabilizations in PSA concentrations were not correlated with the formation of serum IgM or IgG antibodies against PSA; no detectable antibodies were found in 32 of 33 men pre or post vaccination. One patient with stable PSA levels demonstrated production of a low-level titer of antibody to PSA. The inability to detect antibodies to PSA does not necessarily mean that none were generated. It is possible that antibodies could bind circulating PSA and be rapidly cleared by reticuloendothelial cells. Antibodies could also bind to tumor-associated PSA, although PSA is a predominantly secreted protein. In either circumstance, the titer of antibody would be sufficiently low that serum PSA was still readily detectable because an absolute decrease in PSA was infrequent.

This study demonstrates for the first time that PSA can serve as a target for cell-mediated immunotherapy approaches. Prostate cancer patients who expressed elevated serum PSA levels in the absence of symptomatic metastatic involvement tolerated repeated vaccinations with rV-PSA in doses of 2.65 × 10^8 pfu, and certain patients demonstrated PSA peptide-specific cellular responses. A subset of patients have had stabilization of serum PSA levels in the absence of clinical signs of disease progression for up to 25 months. The eventual rise in PSA levels in most patients in this phase I study suggests that immune responses elicited by rV-PSA require boosting. Preclinical studies with recombinant poxviruses expressing CEA have suggested that priming with recombinant vaccinia virus and boosting with recombinant avipox virus elicited greater CEA-specific T-cell responses than with either vector alone (28). This observation is further supported by recent human clinical studies evaluating prime-boost regimens with recombinant vaccinia and avipox viruses expressing CEA (30). These results, combined with the study reported here, have led to the initiation of a phase II clinical trial using a prime and boost administration of rV-PSA and recombinant avipox (fowlpox) virus expressing PSA in patients with prostate cancer.

References

A Phase I Trial of a Recombinant Vaccinia Virus Expressing Prostate-specific Antigen in Advanced Prostate Cancer


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