PROVENGE (Sipuleucel-T) in Prostate Cancer: The First FDA-Approved Therapeutic Cancer Vaccine

Martin A. Cheever and Celestia S. Higano

Abstract

Sipuleucel-T (PROVENGE; Dendreon) is the first therapeutic cancer vaccine to be approved by the U.S. Food and Drug Administration. In men who have metastatic castration-resistant prostate cancer with no or minimal symptoms, sipuleucel-T prolongs median survival by 4.1 months compared with results in those treated with placebo. At 3 years, the proportion of patients in the vaccine group who were alive was 50% higher than that in the control group (31.7% versus 21.7%, respectively). Sipuleucel-T, which is designed to elicit an immune response to prostatic acid phosphatase, uses the patient’s own immune system to recognize and combat his cancer. Currently, no other agents are available that offer a survival benefit for this population of asymptomatic patients who have not been treated with chemotherapy, except for docetaxel (whose inherent toxicities often lead patients and physicians to delay administration until symptoms develop). Straightforward strategies to increase the efficacy of sipuleucel-T are likely to provide even greater benefit. The preclinical and clinical development of sipuleucel-T is reviewed, and approaches to enhance efficacy are considered herein.

Introduction

In April 2010, the U.S. Food and Drug Administration (FDA) approved PROVENGE (sipuleucel-T; Dendreon), an autologous cellular immunotherapy, for the treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T is a therapeutic vaccine that is formulated to stimulate an immune response to prostate cancer cells by targeting prostate acid phosphatase (PAP), a tissue antigen expressed by prostate cancer cells (1). The therapeutic intent is to generate PAP-specific T cells capable of recognizing and killing prostate cancer cells that express PAP. After radical prostatectomy, the major remaining source of PAP in the body is the cancerous prostate tissue. The PAP vaccine immunogen is formulated as PA2024, a fusion protein that combines recombinant PAP with recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF). The PAP-GM-CSF fusion protein is incubated with autologous peripheral blood mononuclear cells (PBMC) obtained by leukapheresis. GM-CSF is used to activate antigen-presenting cells (APC) within the autologous PBMC product (2–5). The activated APCs are capable of activating and inducing replication of PAP-specific immune T cells with the capacity to recognize and kill PAP-positive prostate cancer cells. Three days after leukapheresis and after ~40 hours of incubation, the cells are washed to remove the fusion protein, shipped to the patient care site, and infused into the patient as the sipuleucel-T product.

Preclinical Data

The prostate gland varies greatly among species (6) and immune systems; thus, the results from animal models cannot be directly extrapolated to prostate vaccine trial designs in humans. However, previous studies showed that immunization of rats with rat prostate tissue antigens could induce destructive prostatitis (7), and a formulation using rat APCs loaded with rat PAP plus GM-CSF could induce rat prostatitis (8) without apparent toxicity to normal non-prostate tissues. Both of these studies showed that it is possible to overcome normal immune tolerance and induction of autoimmunity to prostate tissue (7, 8). Although the prostate gland in rats was not totally destroyed by the PAP vaccine, despite induction of autoimmune prostatitis, vaccine induction of prostatitis in rats laid the groundwork for clinical trials of similar vaccines against prostate cancer.

Clinical Studies

Early-phase trials

Sequential phase I and II studies evaluated the safety of the PAP vaccine and the ability to circumvent immune tolerance to PAP (9, 10). Patients in the phase I trial received increasing doses of sipuleucel-T. Those on the phase II protocol received doses totaling their entire leukapheresis
product prepared as sipuleucel-T. Fever was the most common adverse event (AE) and was experienced by 14.7% of the patients. All 31 patients tested (100%) showed an immune response to the fusion protein, PA2024, and 38% showed an immune response to PAP. Time to progression was correlated with both dose and immune response to PAP. With tumor response measured as decreased levels of prostate-specific antigen (PSA; ≥25%) from baseline, tumor response was seen in only 20% of patients. Of note, the fusion protein contains a joining region segment that is not expressed by normal PAP or GM-CSF and can therefore be recognized as foreign by the patient’s immune system. Elicitation of an immune response to this foreign joining region segment is expected and is a sign of immune competence but is most likely irrelevant to the therapeutic outcome. Detection of immunity to PAP is a more important potential marker of therapeutic immune response. An additional efficacy trial that tested a vaccine containing autologous CD54-positive PA2024-loaded APCs provided similar results (11). CD54, also referred to as intercellular adhesion molecule-1 (ICAM-1), is an activation marker for APCs and other leukocytes (12).

Phase III studies
Two phase III studies (D9901 and D9902A) set the stage for the Immunotherapy Prostate Adenocarcinoma Treatment (IMPACT) trial, the pivotal study that led to FDA approval (13, 14). Both were randomized, double-blind, placebo-controlled trials of patients with asymptomatic mCRPC. The designated primary endpoint was median time to observed disease progression, and a secondary endpoint was a planned analysis of overall survival.

The control was autologous PBMCs obtained by leukapheresis, but the PBMCs were cultured without the PAP-GM-CSF fusion protein (i.e., without either antigen or the activating effect of GM-CSF). Only one third of the leukapheresis sample was processed for each dose of the control formulation. The remaining PBMCs were cryopreserved and held in reserve for possible use in a planned salvage vaccine study. The control product was denoted as APC8015F.

For D9901, the median time to disease progression was 11.7 weeks for the sipuleucel-T arm versus 10.0 weeks for the control arm. The curves separated at 8 weeks and showed a persistent separation throughout the rest of the study. However, the difference favoring sipuleucel-T was just short of statistical significance ($P = 0.052$). The median overall survival was 112 weeks for sipuleucel-T compared with 93 weeks for the control arm. The increase in overall survival favoring sipuleucel-T of 4.5 months was statistically significant ($P = 0.01$; refs. 3 and 13).

The positive effect on overall survival appeared to be inconsistent with the lack of a detectable effect on median time to disease progression, suggesting that median time to disease progression might not be appropriate for measuring vaccine effects in patients with very short times to disease progression. Considering that the regimen involved 3 vaccinations, one would not expect the optimum immune response to occur or be operative until the third vaccination (i.e., after 4 weeks of therapy). With a median time to progression of 10 to 11 weeks, the optimum immune response would have only 6 to 7 weeks to operate before the observed progression. The time might be too short to expect a prolongation in time to progression, despite the ultimate demonstration of a vaccine-induced prolongation in median survival. In addition, it is difficult to precisely determine the time to progression in prostate cancer. New lesions on bone scans may be interpreted as progression even when the disease is responding (i.e., the flare phenomenon), and the combination of rising PSA and supposed bone scan progression could erroneously lead to a designation of progression. On the basis of results from this and other immunotherapy trials, the Prostate Cancer Working Group 2 recently devised progression guidelines to prevent this situation (15).

In the second randomized phase III study, D9902A, time to progression was also not statistically different (10.9 weeks versus 9.9 weeks). The median survival was again prolonged in the sipuleucel-T arm compared with the control arm (15.7 months versus 9.0 months, respectively) and survival at 3 years was 50% higher (32.3% versus 21.2%, respectively). Despite the clear benefit in overall survival at 3 years, prolongation of median survival was not statistically significant ($P = 0.331$; refs. 3, 13, and 14). The median time to progression occurred on average only 6 weeks after the third vaccination, ~1 year before the median survival time.

The third randomized phase III trial, D9902B (also called the IMPACT trial), led to FDA approval (16). The primary endpoint was overall survival. IMPACT was a double-blind, placebo-controlled study involving 512 asymptomatic or minimally symptomatic patients with mCRPC randomly assigned 2:1 to sipuleucel-T ($n = 341$) or control ($n = 171$). Sipuleucel-T was administered every 2 weeks for 3 total doses. Of the 330 patients who received sipuleucel-T, 92% received all 3 infusions, versus 93% in the control arm. A comparison of the treatment and control arms shows that the median overall survival was 25.8 months versus 21.7 months, respectively ($P = 0.032$), with a median survival benefit of 4.1 months. The adjusted hazard ratio (HR) for death was 0.78 [95% confidence interval (CI), 0.61–0.98]. The Kaplan-Meier estimate for overall survival for both groups at 36 months was 31.7% versus 23.0%, respectively, indicating a 38% increase in survival at 3 years (ref. 16; Fig. 1).

The Halabi prognostic model can be used to predict individual survival probabilities of patients with metastatic hormone-refractory prostate cancer (17). This model is predicated on factors linked to outcome, including lactate dehydrogenase, PSA, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, hemoglobin, and the presence of visceral disease. The median overall survival predicted by the Halabi prognostic model was 20.3 months for the treatment arm versus 21.2 months for the control arm (3), providing additional support for the efficacy of sipuleucel-T. Among the 3 phase
Sipuleucel-T did not significantly delay cancer progression (defined as PSA reaching 3.0 ng/mL). However, the rate of the PSA increase was slower in patients who received the vaccine. These results support the assumption that the vaccine-induced therapeutic response continues to function after the median time to progression. Changes in PSA doubling times were not reported in the IMPACT trial.

Open-label vaccine in control patients

When progression was determined by central review, it was found that these pivotal trials permitted crossover of placebo patients. This design may have decreased the investigators’ ability to measure the true positive magnitude of the therapeutic effect of sipuleucel-T. The vaccine used to treat placebo patients who crossed over to the open-label vaccine protocol (16) differed in formulation from sipuleucel-T in that the vaccine (APC8015F) was processed from frozen PBMCs collected during the original leukapheresis. Patients could be treated at the time of initial progression or any time thereafter, including after chemotherapy. APC8015F was manufactured according to the same specifications as sipuleucel-T using the PAP-GM-CSF fusion protein. However, fewer total cells were injected. On the control arm, 109 of 171 patients (64%) received therapy with the salvage vaccine, APC8015F. Although those treated with APC8015F had an estimated median survival of 23.8 months versus 11.6 months for those who did not, it is difficult to draw any conclusions regarding efficacy, because therapy was not randomly assigned. The activity of APC8015F has not been prospectively studied.

Approximately 50% of patients in each arm were treated with docetaxel following progression (16); therefore, we can conclude that the difference in survival seen in the sipuleucel-T arm is not due to an imbalance of patients who received docetaxel.

Acute infusion reactions

The majority of patients (71%) experienced acute infusion reactions. Most events were mild or moderate. The

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Table 1. Summary of overall survival results for 3 phase III randomized trials

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>Study D9902B</th>
<th>Study D9901</th>
<th>Study D9902A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median, months (95% CI)</strong></td>
<td>Sipuleucel-T (n = 341)</td>
<td>Placebo (n = 171)</td>
<td>Sipuleucel-T (n = 82)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td>0.775 (0.614, 0.979)</td>
<td>0.568 (0.388, 0.884)</td>
<td>0.786 (0.484, 1.278)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.032a</td>
<td>0.010b</td>
<td>0.331b</td>
</tr>
</tbody>
</table>

Abbreviation: LDH, lactate dehydrogenase.

aTest statistic based on the Cox proportional hazards model adjusted for PSA (1n) and LDH (1n) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade.

bHazard ratio based on the unadjusted Cox proportional hazards model and P values based on an unprespecified test (log-rank).

From Biologics License Application SNT125197 (3).
most common events, which occurred in ≥20% of patients, were chills, pyrexia, and fatigue. These events generally occurred within 1 day of an infusion and were managed on an outpatient basis, and most resolved within 2 days. Severe (grade 3) acute infusion reactions were reported in 3.5% of patients and included chills, fever, fatigue, asth- 

The final sipuleucel-T product is heterogeneous and varies from dose to dose within each patient. Sipuleucel-T was designed as a vaccine composed of mature APCs loaded with PAP; however, the product also contains many other cell types, including T cells, B cells, and natural killer cells. The final mixture of cells depends on the composition of the individual patient’s leukapheresis product and the outcome of processing, both of which change with each subsequent leukapheresis. The product derived from the first leukapheresis is returned for i.v. administration on day 3. To manufacture the second and third doses of sipuleucel-T, the patient undergoes leukapheresis again on approximately days 14 and 28. Although the manufacturing process is identical, the second and third doses are biologically quite different from the first. Each dose contains progressively more activated APCs as well as more PAP-specific T cells with the capacity to recognize and kill prostate cancer cells (20).

Mechanism of Therapeutic Efficacy

The designated purpose of sipuleucel-T is to elicit a therapeutic immune response to PAP expressed by cancer cells. The first treatment primes the immune system. Sipuleucel-T activates APCs ex vivo. The activated APCs facilitate both ex vivo priming of T cells during culture and in vivo priming after administration. After infusion of the first dose, there is a detectable increase in APC and T-cell activation markers in the PBMCs of treated patients and an increase in the ex vivo production of T-cell activation-associated cytokines. Studies that examined cytokine secretion from PBMCs during the culture of each leukapheresis product showed progressive activation of APCs and T cells. An analysis of the culture supernatant from PBMC from each leukapheresis showed increases in cytokine production in the PBMCs of treated patients and correlate PAP-specific immune responses to outcomes that exceeded the designated low value of 400 at any time after baseline were observed in only 43 of 151 patients (28.5%) in the sipuleucel-T arm versus 1 of 70 patients (1.4%) in the placebo arm. At week 6, T-cell proliferation responses (stimulation index >5) to PAP were observed in only 15 of 55 patients (27.3%) in the sipuleucel-T arm versus 2 of 25 patients (8.0%) in the placebo group (16).

Sipuleucel-T prolonged survival, but without a clear demonstration of detectable PAP-specific immunity in the majority of patients. Accordingly, a subset of patients...
without detectable immune responses appeared to benefit from the vaccine. The apparent benefit of the vaccine in patients without detectable immune responses hindered the attempt to correlate outcome to PAP immunity.

A low incidence of detectable antibody response is expected from any activated APC vaccine. The activated APCs in sipuleucel-T are known to process and degrade PAP for presentation to T cells. As a result of the washing process, very little free PAP in protein form (the configuration needed to elicit antibody responses) is injected into patients. The dearth of detectable T-cell responses to PAP may be explained by the fact that responses were assayed from peripheral blood. Peripheral blood may not adequately represent T-cell responses at sites of tumor deposition. Alternatively, it is possible (although unlikely) that substantial numbers of PAP-specific T cells were not activated in most patients, and thus the demonstrated therapeutic effect was not related to or dependent on elicitation of PAP-specific immune responses. Additional studies are needed to determine the proximate mechanisms of efficacy.

One might speculate that mechanisms other than or in addition to the slowing of tumor growth were responsible for the improved outcomes. This raises two questions: Why do patients with prostate cancer die, and what was the proximal cause of death influenced by sipuleucel-T? In general, patients with cancer die of some combination of organ failure, infection, and cachexia. In particular, patients with prostate cancer commonly have dominant pain and cachexia. The proximal cause of death in the sipuleucel-T trials was not reported. However, in general, approximately 60% to 70% of patients with advanced prostate cancer have cachexia (21–23). Several cytokines (e.g., TNFα, IL-1, IL-6, and IL-8) are elevated in patients with prostate cancer and may be involved in cachexia (21). The infusion of activated APCs and T cells, as components of sipuleucel-T, may have substantially perturbed the character and level of these circulating cytokines without noticeably affecting tumor size or growth.

Vaccines

Sipuleucel-T is the first FDA-approved vaccine for cancer. Thus, there is no approved direct comparator vaccine. However, an alternative, well-tolerated, recombinant Poxx-virus-based PSA-targeted vaccine (PROSTVAC-VF; Therion Biologics) currently in development could prove to have substantial efficacy. An overall survival analysis of a phase II, randomized, controlled trial in patients with mCRPC showed a 44% reduction in the death rate and an 8.5-month improvement in median overall survival (24). The data strongly suggest a therapeutic benefit but require confirmation from a phase III study. On the basis of preliminary data, the study investigators hypothesize that patients with more indolent mCRPC (Halabi predicted survival ≥18 months) may best benefit from PSA-specific vaccine therapy (24). As with sipuleucel-T, there was no significant prolongation of median survival.

Chemotherapy

To date, chemotherapy has shown only modest benefit in patients with mCRPC. In 2 phase III studies [TAX 327 and Southwest Oncology Group 9916], docetaxel-based regimens showed a survival advantage (25, 26). In TAX 327, the pivotal trial for docetaxel approval, the median survival was 18.9 months in the every-3-weeks docetaxel arm compared with 16.4 months in the mitoxantrone arm, with an HR of 0.76 or a 2.5-month improvement in median survival (25). The most significant grade 3 and 4 AEs were neutropenia (32%), infection (6%), anemia (5%), sensory neuropathy (2%), motor neuropathy (2%), nausea (3%), diarrhea (2%), vomiting (2%), dyspnea (3%), fatigue (5%), and arthralgia (1%). Patients reported lower-grade but nonetheless disturbing side effects of fluid retention (24%) with peripheral edema (18%) and weight gain (8%), and sensory neuropathy (30%), motor neuropathy (7%), alopecia (65%), nail changes (41%), diarrhea (32%), stomatitis/pharyngitis (20%), taste disturbance (18%), nausea (17%), and fatigue (53%). In the supporting phase III SWOG 9916 trial, the median survival advantage was 1.9 months (17.5 months for the docetaxel plus estramustine arm versus 15.6 months for the mitoxantrone plus prednisone arm) with an HR of 0.80 (26). Given these modest survival data and the toxicity profile of docetaxel, it is clear why both patients and physicians are reluctant to use chemotherapy in men who have no or few symptoms related to mCRPC.

Conclusions

At the present time, sipuleucel-T is the only therapy that is specifically approved for men with asymptomatic or minimally symptomatic mCRPC. The very acceptable toxicity profile makes sipuleucel-T an attractive option for such patients, particularly in comparison with docetaxel. Although a significant proportion of patients taking sipuleucel-T will undoubtedly receive docetaxel at a later stage in the disease, the availability of a therapy that can improve survival at an earlier stage is a welcome addition to treatment options for patients with mCRPC. Guidelines from the National Comprehensive Cancer Network now include sipuleucel-T in the treatment options for men with mCRPC with no or minimal symptoms (27).

One of the current challenges of sipuleucel-T therapy is determining when in the course of prostate cancer it should be used. The FDA-approved package insert states that sipuleucel-T “is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.” The label gives little additional guidance for use. Specifically, patients treated with chemotherapy are not excluded from receiving sipuleucel-T, yet many such patients continue on low-dose prednisone as a component of their prior chemotherapy. Because of its potential detrimental effects on the immune system, corticosteroid use was excluded in the clinical trials,
and hence should be stopped before treating a patient with sipuleucel-T. In general, sipuleucel-T should be administered before chemotherapy, except in cases where the disease remains stable after chemotherapy without the use of steroids.

It is anticipated that abiraterone, an investigational CYP17 inhibitor, will be approved by the FDA in 2011. Abiraterone has been studied in two phase III trials that are fully accrued and maturing [one in asymptomatic patients who have not yet received docetaxel (COU-AA-301) and the other in patients previously treated with docetaxel (COU-AA-302)]. The basis for this phase III program was the significant activity seen in early-phase trials (28–30). Recently presented interim results for COU-AA-302 (31) showed that abiraterone plus prednisone was superior to placebo plus prednisone in terms of overall survival (14.8 months versus 10.9 months, HR = 0.65), the primary endpoint. On the basis of these results, regulatory approval is anticipated for abiraterone in patients who have received docetaxel. Given the survival benefit seen in patients who have received chemotherapy, it is anticipated that COU-AA-301 will also be positive, leading the way for approval in the asymptomatic CRPC population for which sipuleucel-T is also approved.

Assuming that abiraterone will eventually be approved by the FDA for patients with asymptomatic CRPC either before or after docetaxel treatment, it is important to consider the appropriate timing of sipuleucel-T administration with respect to abiraterone. Because abiraterone was studied in combination with low-dose prednisone, approval will include concurrent use of prednisone to prevent the mineralocorticoid effects of hypertension and hypokalemia seen in some patients on abiraterone alone. Because abiraterone must be administered with prednisone, it seems logical to assume that sipuleucel-T should be administered before abiraterone, and that the administration of any therapy that includes prednisone should be delayed for as long as possible due to the immunosuppressive effects of corticosteroids. Although some results in the literature suggest that abiraterone can be given without prednisone (32), its use as a single agent is not advised until better data are presented and guidelines about this practice are developed.

A confusing issue for patients and clinicians alike is the lack of the usual response indicators after administration of sipuleucel-T. Neither the PSA level nor the time to progression was significantly affected by sipuleucel-T. Therefore, there should be no expectation that PSA will decline or that imaging studies will improve after treatment. The lack of response indicators also means that physicians cannot advise an individual patient as to whether he has benefited from receiving sipuleucel-T; they can only explain that there is a population benefit in terms of overall survival. This is similar to the logic used in adjuvant therapy of breast or colon cancers. In addition, sipuleucel-T is not indicated for the treatment of patients who have symptoms of metastatic disease. At this writing, there is no evidence of survival benefit or indication of palliative benefit of sipuleucel-T given as a single agent to patients with symptomatic mCRPC.

Clinical development of sipuleucel-T for FDA approval began after the first patient was treated in 1997. Thus, the formulation and regimen have been “locked” and unchanged for 13 years. In this locked regimen, 3 doses of sipuleucel-T are administered over a period of ~4 weeks. Given the comparative efficacy and limited toxicity of this agent, studies to increase the efficacy of sipuleucel-T are warranted. Simple methods that are likely to increase efficacy include (i) administering sipuleucel-T >3 times to boost and extend the response; (ii) treating patients earlier in their disease course, thus extending the immune response time against a lower number of cancer cells; and (iii) combining sipuleucel-T with agents that are known to activate, accelerate, and augment immune responses. Multiple strategies involving targeted agents might also have substantial effects by facilitating T-cell entry into tumors and thus enhancing efficacy. In one study (33), investigators combined the vaccine with bevacizumab in patients after definitive therapy, but the study was too small and the single-arm design precluded insights into how the agents combine.

Immunotherapy agents with known immunologic efficacy that could likely increase the efficacy of sipuleucel-T include T-cell growth factor (IL-7) to increase the number and repertoire of naïve T cells, T-cell growth factor (IL-15) to increase the growth and survival of immune T cells, growth factors (Flt-3 Ligand) to increase the number of APCs, agonists to activate dendritic cells and other APCs (CD40 Ligand), adjuvants (IL-12, cytosine phosphorothioate guanine, and monophosphoryl lipid) to augment T-cell responses, agonists to activate and stimulate T cells (anti-CD137), inhibitors of T-cell checkpoint blockade (anti-CTLA4 and anti-PD1), and agents to inhibit, block, or neutralize cancer cell– and immune cell–derived immunosuppressive cytokines (anti–IL-10, anti-TGF-β, and 1-methytryptophan). These and similar agents in the same categories have been discovered, invented, or constructed, and shown to have immunologic function in both animal models and human clinical trials (34). In the past, a variety of regulatory and legal hurdles have made it extremely challenging, if not impossible, to combine investigational immunotherapeutic agents owned by different sponsors. With the commercial availability of sipuleucel-T and perhaps other promising vaccines in the future, we can proceed to test and develop agents designed to activate, augment, and extend immune responses, with the hope of refining and improving immunotherapeutic outcomes in patients with prostate cancer and other solid tumor malignancies.

Disclosure of Potential Conflicts of Interest

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