Sipuleucel-T: A New Advance in the Treatment of Castrate-Resistant Prostate Cancer

ROBERT IGNOFFO, PharmD, FASHP, FCSHP

From Touro University, Mare Island, California.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Robert Ignoffo, PharmD, 1310 Johnson Lane, Mare Island, Vallejo, CA 94592; E-mail: Robert.Ignoffo@tu.edu

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Prostate cancer ranks as the second most common malignancy in men with approximately 217,700 new cases in 2010 (Jemal, Siegel, Xu, & Ward, 2010). Although early-stage prostate cancer has a good prognosis and long survival, about 20%–30% of cases recur with advanced disease. Although androgen deprivation therapy to castrate testosterone levels is the most common treatment approach and is often effective in this setting, resistance eventually occurs. Castrate-resistant prostate cancer (CRPC) is virtually incurable and has a median survival that ranges from 12–22 months (Di Lorenzo, Autorino, Figg, & De Placido, 2007).

Chemotherapy using docetaxel (docetaxel-based combination) and prednisone was the first treatment to demonstrate a survival benefit. This regimen produced about a 19-month median survival, about a 2.4-month improvement over the previous standard therapy but came with substantial bone marrow and neurologic toxicities (Berthold et al., 2008). More effective and less toxic therapies would fill a very important need for clinicians managing advanced asymptomatic prostate cancer.

Development of Sipuleucel-T

RATIONALE FOR VACCINE DEVELOPMENT

Although prostate cancer is not traditionally thought to be amenable to immunotherapy, several studies suggest otherwise. It is very slow-growing, which would allow ample time for a stimulated immune system to have an antitumor effect (Antonarakis & Drake, 2010). Prostate cancer can induce autoantibodies. Active immunotherapy combined with immune checkpoint blockage (using low-dose chemotherapy), androgen blockade, or radiation therapy can produce an antitumor response. (Arlen, Mohebtash, Madan, & Gulley, 2009; Drake, Jaffee, & Pardoll, 2006). Lastly, studies in patients with recurrent prostate cancer demonstrate increased tumor tissue specific-antigens including prostate specific-antigen (PSA) and prostatic acid phosphatase (PAP; Rhodes, Barrette, Rubin, Ghosh, & Chinnaiyan, 2002; Taylor, Varambally, & Chinnaiyan, 2006). Furthermore, the small tumor burden in those patients who develop PSA relapse after prostatectomy or radiation therapy makes them good candidates for immunotherapy.

Dendritic cell-based vaccines with

incorporated tumor-related antigens or proteins can target prostate cancer that overexpresses tumor antigens, including PSA and PAP. (Small et al., 2000). Thus, an active specific immunotherapy using vaccine technology is rational and has led to the development and recent approval of sipuleucel-T (APC 8015, Provenge). Phase III studies evaluating new vaccines such as sipuleucel-T and poxviral vector vaccine (ProstVac) have been recently completed. Sipuleucel-T was approved by the U.S. Food and Drug Administration (FDA) on April 29, 2010, for advanced asymptomatic androgen-independent prostate cancer which is the topic for the rest of this article.

MECHANISM OF ACTION

Although its precise mechanism of action is unknown, sipuleucel-T is designed to induce an immune response targeted at PSA and PAP, antigens expressed in about 95% of prostate cancers (Higano et al., 2007). Autologous antigen-presenting–cells (APCs) are vital to the activation and expansion of CD-8+ T cells. Dendritic cells (DC) are potent APCs that are enhanced in effect in the presence of interleukin 1, tumor necrosis factor-α, or granulocyte-macrophage colony-stimulating factor (GM-CSF). Sipuleucel-T incorporates autologous DCs, GM-CSF and PAP (also known as PA2024). PA2024 promotes efficient processing of APCs on prostate cells and is required to enhance the immune T-cell response to the antigen-loaded DCs. A simplified diagram of this immunotherapy is shown in Figure 1.

CLINICAL STUDIES

A phase I/II study of 31 patients treated with sipuleucel-T demonstrated both clinical responses and a very good safety profile (Small et al., 2000). In the phase II portion of this study, 19 patients with nonmetastatic disease but a rising PSA level were treated with sipuleucel-T. Six of 31 patients obtained at least a 25% reduction in PSA value. Treatment was well tolerated, with fever occurring in about 15% along with mild myalgia, fatigue, and urinary symptoms.

On the basis of a 25% PSA response and a favorable toxicity profile, two phase III studies (Dendreon, D9901, D9902A & B) were designed and carried out from January 2000 through March 2003. Study D9901 was performed in 127 patients with metastatic, asymptomatic prostate cancer across the United States from January 2000 to October 2001 (Small et al., 2006). One hundred and fifteen patients had progression of

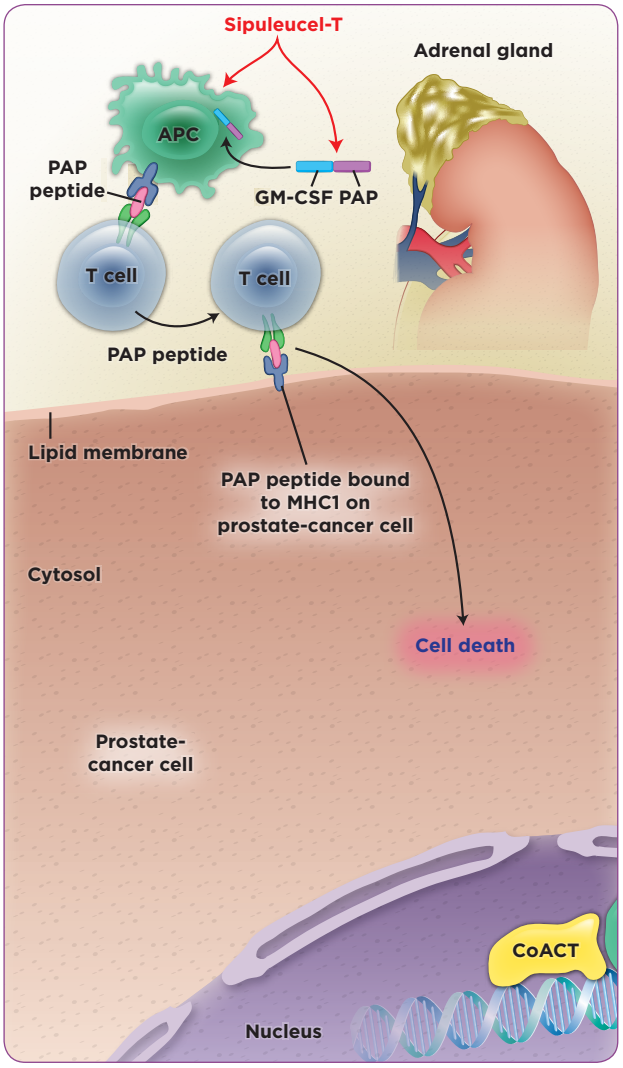

Figure 1. Graphic representation of sipuleucel-T mechanism of action. It is a cell-based vaccine created by exposing autologous antigen-presenting peripheral blood mononuclear cells (APCs; enriched from a dendritic cell fraction) to a recombinant protein consisting of granulocyte-macrophage colony-stimulating factor (GM-CSF) fused to prostatic acid phosphatase (PAP). When the now specifically immunocompetent cells are reintroduced into the patient, the hope is that an antitumor T-cell response will be generated against tumor cells expressing PAP. MHC1 = major histocompatibility complex 1; CoACT = androgen receptor coactivator. Source: Longo (2010).

disease but no systemic symptoms (bone pain, cancer pain, or visceral disease). All patients were required to have positive immunohistochemistry staining for PAP in at least 25% of prostate cancer cells. Patients were treated using a 2:1 randomization of sipuleucel-T to placebo. The primary endpoint was time to tumor progression (TTP) defined as new pain, bone fracture, and nerve root or spinal cord compression. Secondary endpoints were overall survival, 3-year overall survival, T-cell stimulation, and adverse drug effects. Patients were given infusions of sipuleucel-T or control mononuclear cells at 0, 2 and 4 weeks (Small et al., 2006).

The results of this study were interesting, with the median TTP being 11.7 weeks for sipuleucel-T and 10 weeks for placebo, which was not significant (p = .052). Surprisingly, median overall survival was 25.9 months for sipuleucel-T compared with 21.4 months for placebo and was significant (p = .01). Furthermore, overall survival at 3 years was 34% (28/82) for sipuleucel-T–treated patients compared withn 11% (5/45) for placebo-treated patients (p = .005). The survival benefit persisted after correction for PSA, lactate dehydrogenase, number of bone lesions, body weight, and local disease. Stimulated CD-8+ T cells were eight-fold higher in sipuleucel-T–treated patients. Progression of disease occurred in 90% of patients at 36 months (115/127). About 75% of those randomized to receive placebo were allowed to cross over to sipuleucel-T. About 48% of patients who had progressed on sipuleucel-T were treated with subsequent docetaxel-based chemotherapy compared with 35% of those who had progressed on placebo.

Study D9902A randomized 98 men with asymptomatic CRPC to sipuleucel-T (n = 65) or placebo (n = 33). This study also showed no significant improvement in TTP or overall survival at 3 years (p = .33). However, a post-hoc analysis of both studies showed that there was a significant survival advantage for the vaccine-treated group (HR, 0.68, p = .01; Higano et al., 2007).

Despite these results, the FDA denied approval of sipuleucel-T in May 2007 because the primary endpoint in both D9901 and D9902A was TTP and not survival and requested further study. This conclusion was reached despite the FDA's own advisory committee overwhelmingly recommending its approval. Fortunately, another phase III study (IMPACT) was ongoing using overall survival as the primary endpoint and has been recently published (Kantoff et al., 2010).

The IMPACT trial accrued 512 patients and was completed in 2007. Patients were randomized to receive 3 doses of sipuleucel-T (n = 341) or placebo (n = 171), both given at 2-week intervals. Patients were allowed to be crossed over to docetaxel therapy. The results of this study were presented in March 2010 at the Genitourinary Cancer Symposium in San Francisco. With a median follow-up of 36.5 months, the data demonstrated a modest but real overall survival advantage of 25.8 compared with 21.7 months for the vaccine-treated group over the placebo group (HR, 0.76; p = .03; Kantoff et al., 2010). Outcomes were consistent across several subgroups analyzed. The 3-year survival was 32% for the vaccine-treated group and 23% for the placebo group. The authors noted that these data were similar to those of another randomized trial, in which the vaccine group had a 3-year survival rate of 34.1%, a survival of 25.9 months and an increased survival time of 4.5 months (Small, et al., 2006). In contrast to survival, TTP was no different in each of the study groups, which is also consistent with other studies (Small et al., 2006; Higano et al., 2007). This is a surprising result considering that the drug did not demonstrate an objective tumor response and has raised concerns about whether a predisposing factor may have accounted for the difference in survival.

In an editorial by Dan Longo in the same issue as the published article, he identified a potential factor in the IMPACT study, specifically the preparation of the placebo, which contained cultured APCs alone rather than APCs plus GM-CSF (Longo, 2010). A better placebo would have been the use of cultured antigen plus GM-CSF without the antigen PAP (Longo, 2010).

ADVERSE EFFECTS

Sipuleucel-T was generally well tolerated with the majority of adverse effects being related to cytokine release. Infusion reactions were common-occurring in about 71% of patients with 3.5% of patients having severe reactions (Kantoff et al., 2010; Provenge Package insert, 2010). Grade 1 or 2 reactions included fever, chills, headache, myalgia, hypertension, hyperhydrosis, and groin pain and confirmed the safety profile of earlier studies. Because the final product contains natural killer

Table 1. **Indication, dosing, administration, and adverse effects of sipuleucel-T**

Indication	Asymptomatic, advanced prostate cancer refractory to hormonal therapy
Dosage form	Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP–GM-CSF, suspended in 250 mL of lactated Ringer's solution.
Premedication	Oral acetaminophen (650 mg PO) and diphenhydramine (25 mg IV or PO), both 30 minutes prior to administration of sipuleucel-T
Dose	5×10^6 autologous mononuclear cells
Administration	Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag. Once the patient is prepared for infusion and the Cell Product Disposition Form has been received, remove the sipuleucel-T infusion bag from the insulated container and inspect the bag for signs of leakage. Contents of the bag will be slightly cloudy, with a cream-to-pink color. Gently mix and resuspend the contents of the bag, inspecting for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing. Do **not** administer if the bag leaks or if clumps remain in the bag. Infuse sipuleucel-T intravenously over a period of approximately 60 minutes. Do **not** use a cell filter.
Schedule	Every 2 weeks times 3 doses.
Adverse effects	Infusion reactions: In controlled clinical trials, 71% of patients in the sipuleucel-T group developed an acute infusion reaction. The most common events (≥ 20%) were chills, fever, and fatigue. In 95% of patients reporting acute infusion reactions, the events were mild or moderate. Interrupt or slow infusion for acute infusion reactions, depending on the severity of the reaction. The most common systemic adverse reactions (incidence ≥ 15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

Note. From the Provenge Package Insert, May 2010, Dendreon Corporation, Seattle, WA.

cells, T cells, B-cells, and other cells, infusion reactions commonly occur and should be expected. To prevent or minimize infusion reactions, prophylactic diphenhydramine and acetaminophen should be administered 30 minutes prior to giving sipuleucel-T.

PRACTICE AND COST CONSIDERATIONS

The manufacturer of sipuleucel-T, Dendreon, spent about $1 billion on its development. The company states that three infusions of sipuleucel-T will cost $93,000 or about $23,000 per month of life extended by the therapy (Longo, 2010). This expensive therapy will be covered by Medicare Part B (see page 31), which reimburses the cost of any FDA infusion or injection drug, such as sipuleucel-T. Individuals under the age of 65 will be covered by their private insurers and will be subject to high copayments. According to Mitchell H. Gold, M.D., president and chief executive officer of Dendreon, "within the first year of FDA approval, Dendreon anticipates being able to manufacture enough Provenge to support the treatment of about 2,000 patients." (SeniorJournal.com, 2010). The first patient was treated with the commercial product in May 2010.

PREPARATION, ADMINISTRATION AND TECHNICAL ASPECTS

Sipuleucel-T is an autologous product requiring leukapheresis to produce adequate mononuclear cells with DCs for activation by the recombinant protein PAP plus GM-CSF (PA2024). This process takes about 48 hours and will have a stated expiration date and time on the patient's personalized infusion bag. It should be stressed that both the physician and patient should adhere firmly to the leukopheresis schedule. Sipuleucel-T should be infused intravenously over 60 minutes without the use of any inline filter. It may be administered in an outpatient setting.

Implications for the Advanced Practitioner in Oncology

With the approval of sipuleucel-T, advanced practitioners (APs) have a unique option to treat

a specific group of patients with CRPC. However, the AP should be aware of not only the administration aspects of this new agent, noting the potential for infusion reactions and the need to educate both patients and nursing staff regarding management of side effects, but the cost considerations. The AP should be prepared to discuss the issue of cost with the patient and strategies to manage this cost if individual coverage is lacking.

Summary

Sipuleucel-T is the first immunotherapeutic agent to demonstrate an improvement in survival for patients with advanced asymptomatic prostate cancer and should be considered a major advance and potentially paradigm-changing agent. The dosing and administration of sipuleucel-T are summarized in Table 1.

DISCLOSURES

The author has no potential conflicts of interest to disclose.

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