

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

## Immunotherapeutic Approaches in Prostate Cancer: PROVENGE

Nancy Dawson, MD  
 Director of Clinical Research  
 Lombardi Comprehensive Cancer Center  
 Georgetown University  
 Washington, DC

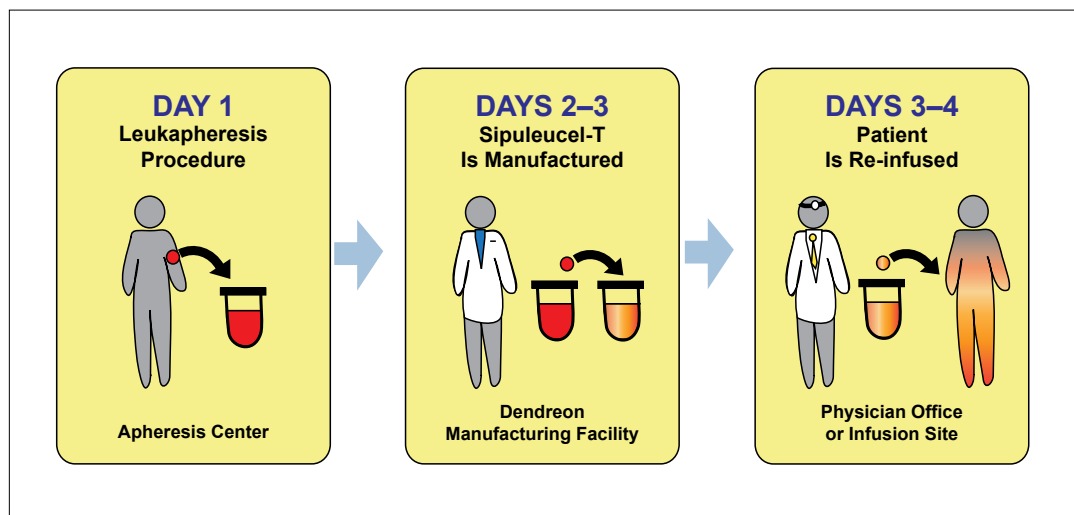
**H&O** What is the current state of therapy for patients with advanced prostate cancer?

**ND** At present, metastatic prostate cancer is treated with androgen deprivation therapy; however, this type of therapy is only effective in controlling the disease for 1–1.5 years, at which point the patient usually experiences disease progression. This is referred to as *castrate-resistant prostate cancer*. The treatment for castrate-resistant prostate cancer is variable; however, most patients receive a second-line hormonal therapy in order to lower the androgens in their body. Subsequent treatment prior to the approval

of sipuleucel-T (Provenge, Dendreon) included docetaxel chemotherapy. The average patient with castrate-resistant prostate cancer treated with the various therapies lives approximately 21 months. There are also new agents in development as second-line hormonal therapies, such as abiraterone.

**H&O** What is immunotherapy and how is it different from other treatment options? What is sipuleucel-T?

**ND** Sipuleucel-T is a new autologous cellular immunotherapy that was approved by the US Food and Drug Administration in April of this year. This new class of therapy is changing how we treat prostate cancer; it is different from chemotherapy, which kills dividing cells, and different from hormonal therapy, which deprives the tumor of androgen. Immunotherapy is based on promoting T-cell proliferation in order to attack the prostate cancer cell. This process is done by leukapheresing a patient (removing blood from the body) to remove



**Figure 1.** The process of sipuleucel-T formulation.

antigen-presenting cells. These cells are then combined with recombinant prostatic acid phosphatase antigen—made by 90% of prostate cancer tumors—and the antigen is then processed and presented on to the surface of the antigen-presenting cell. This fully activated antigen-presenting cell is called *sipuleucel-T*. It is infused into the patient 3–4 days after he has been leukapheresed (Figure 1). The sipuleucel-T activates T-cells in the body that proliferate and attack cancer cells. Clinical trials that evaluated T-cell mediated immune response saw an increased response in patients treated with sipuleucel-T compared to those treated with placebo.

### H&O What key studies led to the approval of sipuleucel-T?

**ND** There were 3 phase III trials that led to the approval of sipuleucel-T. The first 2 trials were relatively small. The first study, D9901, was a double-blind, placebo-controlled trial conducted in the United States evaluating sipuleucel-T in men with asymptomatic, metastatic, androgen-independent prostate cancer. In this study, 127 patients received sipuleucel-T or placebo, with treatment given as 3 infusions every 2 weeks. In this study, patients who received sipuleucel-T had a median survival of 25.9 months compared to 21.4 months for patients receiving placebo—a survival benefit of 4.5 months.

The second study, D9902A, evaluated sipuleucel-T in 98 patients. This study showed that patients receiving treatment had a median survival of 19 months compared to 15.7 months for patients receiving placebo (3.3 month survival benefit). The third study, IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment), was the largest, with 512 patients randomized 2:1 to receive sipuleucel-T or placebo. This trial showed a survival benefit of 4.1 months, with patients on sipuleucel-T reaching a median survival of 25.8 months compared to 21.7 months in the placebo arm. The integrated results of the 3 trials produced an overall survival benefit of 3.9 months, which was the basis of the approval of this agent. It is important to note that this therapy is somewhat different from traditional cancer treatments; the studies evaluating sipuleucel-T did not find an increase in progression-free survival or a decrease in tumor size or prostate specific antigen (PSA) level, but they did see a survival benefit. Why the drug had this effect is not known, but it was consistent across all 3 trials.

### H&O Are there any contraindications to sipuleucel-T? Who is the ideal candidate for this agent?

**ND** There are no contraindications to this therapy, and patients do not have to be evaluated for renal or liver

function. The patients that were included in the clinical trials and are able to receive the therapy are those who are asymptomatic or minimally symptomatic with castrate-resistant prostate cancer and metastatic disease. All these criteria must be met in order to receive sipuleucel-T. The ideal candidate is someone who has progressed on second-line hormonal therapy but is asymptomatic or minimally symptomatic. For most patients, sipuleucel-T would be given between second-line hormonal therapy and chemotherapy, but not concurrently with any other treatment. The patients included in the 3 trials were allowed to have had previous chemotherapy; therefore, sipuleucel-T can be administered outside of a clinical trial in a patient who has had prior exposure to chemotherapy. Currently, the availability of this therapy is limited; however, there are plans to test the drug earlier in the disease course. Patients with a more rapid progression of their cancer or those who have symptomatic disease are recommended to proceed to chemotherapy without receiving sipuleucel-T.

### H&O What are the common toxicities seen with this agent?

**ND** Sipuleucel-T is a well-tolerated therapy. The most common toxicity is a flu-like syndrome. In the IMPACT trial, approximately 50% of patients experienced chills, 30% had a fever, 16% had a headache, and 10% developed a flu-like illness; a slight increase in blood pressure was also observed. These toxicities are short-lived (less than 24 hours) and similar to what one would see with a vaccination or blood transfusion. Patients were premedicated with acetaminophen and diphenhydramine in order to avoid the flu-like symptoms, and most people tolerated the therapy very well.

### H&O With the use of sipuleucel-T, each regimen must be tailored to the patient by a formulation process. Are there any limitations to this process?

**ND** When patients go to an apheresis center to undergo leukapheresis, they can go to a cancer center such as the one here at Georgetown University. The blood is then sent to a processing center, and 3–4 days later, patients come back for re-infusion of their own cells. The main challenge is processing each patient's blood. At present, Dendreon has a limited number of centers to carry out the formulation process. They have a capacity to handle 1–2 patients per site per month, with 50 centers currently operating. Now that the therapy is approved, Dendreon will be building more centers and increasing their resources to handle a larger capacity of patient samples.

**H&O** Since sipuleucel-T does not cure or reduce progression, but extends survival, what contribution will this agent make to the armamentarium of prostate cancer treatments?

**ND** In prostate cancer, there is only 1 approved therapy associated with a survival benefit for castrate-resistant disease—docetaxel chemotherapy—which improves survival by 2.7 months. With sipuleucel-T, we see a survival benefit of approximately 4 months. This increase in survival is important to patients, especially since the extra months of life can be added on to what patients achieve with docetaxel. Furthermore, there are patients who do not want to receive chemotherapy because of the associated toxicity or want to delay it. For these patients, a therapy like sipuleucel-T, which may cause mild flu-like symptoms for approximately 24 hours, with an administration schedule of 3 infusions, is a relatively simple and less toxic therapeutic option. Therefore, sipuleucel-T is a very useful addition to prostate cancer treatments.

**H&O** What effect do you think the approval of this immunotherapy agent will have on future drug development?

**ND** This is the first immunotherapy approach that has been shown to successfully prolong survival in

prostate cancer. Some of the previous immunotherapeutic approaches, including the GVAX (GM-CSF gene transduced allogeneic vaccine) prostate cancer vaccine, have only had marginal or even worse outcomes, so this approval has heightened the awareness that immunotherapeutic approaches may have a role in the treatment of men with prostate cancer. I think we will be seeing more investigations in this type of therapy in the future, specifically trials looking at immunotherapy earlier in the disease course. Other vaccines are currently in development as well. One such vaccine, PROSTVAC-VF (Prostate Vaccine-VF), has undergone phase II testing and is moving into phase III studies in the fall. It uses a virus that has been genetically modified to contain PSA.

### Suggested Readings

Lassi K, Dawson NA. Update on castrate-resistant prostate cancer: 2010. *Curr Opin Oncol*. 2010;22:263-267.

Kantoff P, Higano CS, Berger ER, et al. Updated survival results of the IMPACT trial of sipuleucel-T for metastatic castration-resistant prostate cancer (CRPC). Paper presented at the 2010 Genitourinary Cancers Symposium; March 5-7, 2010; San Francisco, CA.