Optimizing the Efficiency and Quality of Sipuleucel-T Delivery in an Academic Institution

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Background: Sipuleucel-T, an autologous cellular immunotherapy, is approved for the treatment of certain patients with metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T is the first personalized treatment for prostate cancer to be manufactured using the immune system of each individual patient. Patient preparation and compliance are critical because patients undergo serial leukapheresis and reinfusion procedures within a relatively short time period, which may result in transient reactions.

Objectives: The study aims to identify patients best suited for sipuleucel-T treatment, provide an overview of treatment, and encourage infusion sites to consider a primary contact model for the efficient coordination of care.

Methods: Treatment experiences were evaluated from 124 patients with mCRPC who received sipuleucel-T from January 2010 to August 2013 according to current best practices. Feedback was collected from reflective interdisciplinary discussion within the sipuleucel-T delivery team (nurses, advanced practice providers, urologists, and medical oncologists).

Findings: Early patient identification and education on treatment rationale, delivery, and expectations help ensure a successful sipuleucel-T treatment experience. A multidisciplinary coordinated-care process can facilitate proficient sipuleucel-T delivery, and the selection of a primary contact for care coordination offers benefits, such as clear and efficient education.

Sipuleucel-T is an autologous cellular immunotherapy approved by the U.S. Food and Drug Administration (FDA) in April 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant (previously termed “hormone-refractory”) prostate cancer (mCRPC) (Dendreon Corporation, 2010). Sipuleucel-T is unique in its field as the first personalized treatment for prostate cancer manufactured using the immune system of each individual patient (Drake, 2010).

Research on sipuleucel-T has demonstrated statistically significant improvement in overall survival in men with asymptomatic to minimally symptomatic mCRPC being treated with sipuleucel-T. In the phase III Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial, sipuleucel-T improved median survival by 4.1 months (25.8 months with sipuleucel-T versus 21.7 months with placebo), improved three-year survival by 38%, and reduced the relative risk of death by 22% compared with placebo (p = 0.03) (Kantoff et al., 2010) (see Figure 1).

An integrated analysis of two earlier phase III trials also indicated that sipuleucel-T was associated with a significant survival benefit (Higano et al., 2009; Small et al., 2006). However, neither study demonstrated a difference between sipuleucel-T and...
placebo with respect to time to progression or prostate-specific antigen (PSA) response rate (Di Lorenzo, Ferro, & Buonerba, 2012; Higano et al., 2009; Kantoff et al., 2010; Small et al., 2006). In an exploratory analysis of the IMPACT trial, which evaluated treatment effect patterns using baseline PSA quartiles, patients with lower baseline PSA values and less-advanced disease had a greater survival benefit with sipuleucel-T treatment (Schellhammer et al., 2013).

Sipuleucel-T is generated from the patient’s peripheral blood mononuclear cells, which are extracted via a standard leukapheresis procedure that involves filtering the patient’s blood by density-gradient centrifugation (Drake, 2010). By incubating these cells with PA2024, a fusion protein comprised of prostatic acid phosphatase (PAP), and the immune cell activator granulocyte-macrophage colony-stimulating factor (GM-CSF) for 36–44 hours (Kantoff et al., 2010), the patient’s naive antigen-presenting cells (APCs) are activated to recognize the prostate cancer antigen PAP (Sheikh et al., 2013). PAP is present on the majority of prostate cancer cells (Goldstein, 2002; Haines, Larkin, Richardson, Stirling, & Heyderman, 1989). Once infused into the patient’s body, the activated APCs stimulate naive CD4-positive and CD8-positive T-cells to recognize and attack prostate cancer cells expressing PAP (Drake, 2010) (see Figure 2). Because the unique sipuleucel-T manufacturing process requires patients to undergo serial leukapheresis and reinfusion procedures (which are associated with transient reactions) within a relatively short time period, patient preparation and compliance are critical.

From May 2010 to December 2013, Duke University Medical Center treated 138 patients with mCRPC using sipuleucel-T. During that time, the authors of the current article were instrumental in developing a multidisciplinary coordinated care process to optimize the efficiency and quality of sipuleucel-T delivery, including best practices for patient education. This article outlines the authors’ experiences by highlighting key teaching points with the aim of enhancing sipuleucel-T treatment delivery. Because very little guidance currently exists on the practical use of sipuleucel-T for clinics, the current findings may aid other facilities to streamline their practices.

**Pretreatment**

**Sipuleucel-T Eligibility Criteria**

At Duke University Medical Center, sipuleucel-T is offered to men with mCRPC who are asymptomatic or minimally symptomatic (i.e., not requiring opioid analgesics for cancer-related pain) and free of liver metastases, following the FDA label (Dendreon Corporation, 2010) and National Comprehensive Cancer Network ([NCCN], 2013) guidelines. To be eligible for treatment, the patient must have a serum testosterone level of less than 50 ng/dl and evidence of bone and/or nodal metastases. The goal is to treat patients early in this disease state when they have a low tumor burden and have received limited prior therapy; however, any patient with asymptomatic or minimally symptomatic mCRPC is eligible for sipuleucel-T treatment. For patients who have received chemotherapy or secondary hormone agents such as abiraterone acetate, both of which are given with low-dose prednisone, waiting three months from chemotherapy and 30 days from systemic steroids before starting sipuleucel-T is preferential. This conforms with the eligibility requirements for the IMPACT trial (Kantoff et al., 2010; NCCN, 2013). Scheduling of sipuleucel-T reflects current best practice, but it should be noted that ongoing clinical trials to determine alternative sequencing and combinations with other agents may influence treatment approaches in the future. Treatment at Duke University Medical Center is summarized in Figure 3, which also outlines important topics for patient education at key points throughout the process.

**Preparing the Patient**

Potential recipients of sipuleucel-T treatment are first identified by the urology and oncology care team and referred to the coordinating advanced practice provider (APP), who ensures their suitability. The APP becomes their primary contact throughout the treatment process and is responsible for coordinating care, patient education, and management. Two APPs were involved in the implementation of the authors’ algorithm on the sipuleucel-T treatment delivery process and accompanying patient education.

After confirming that the patient is a candidate for treatment with sipuleucel-T, the APP initiates a discussion with the patient, either during clinic visit or by telephone, regarding the treatment process. Because sipuleucel-T is significantly different from other therapies in mechanism of action and treatment delivery, explaining the leukapheresis and infusion processes, patient responsibilities, and treatment expectations during the initial discussion is important. First, the APP explains the nature
of sipuleucel-T as a personalized treatment manufactured using components of the immune system of each patient (Drake, 2010). Building on this description of how sipuleucel-T works, the APP explains that, unlike cytotoxic chemotherapies and hormonal agents approved in mCRPC, sipuleucel-T does not have an immediate antitumor effect and, therefore, the short-term change in PSA does not reflect treatment response for sipuleucel-T (Di Lorenzo et al., 2012). Importantly, the APP advises the patient that PSA may increase during and after sipuleucel-T treatment and subsequent therapy will be determined based on clinical and/or radiographic progression. The APP further highlights that sipuleucel-T treatment does not result in an immediate response by radiographic measurements and that, in most cases, progression on scans can be seen over time. This does not reflect treatment failure. Rather, because of the presumed mechanisms of action that engage the immune system, the clinical benefit of sipuleucel-T is delayed.

The APP also discusses how sipuleucel-T fits into the treatment schema for advanced prostate cancer, including why androgen-deprivation therapy continues alongside sipuleucel-T, and what treatments may follow sipuleucel-T, such as abiraterone acetate, enzalutamide, docetaxel, or other therapies.

Costs and Travel

Patients often are concerned about treatment costs, and this should be discussed up front along with insurance coverage and travel assistance for eligible patients. A careful review of insurance benefits is completed by a Duke Financial Care Counselor and Dendreon-On-Call representative to complete prior authorizations (when required) and inform patients of any anticipated out-of-pocket expenses before they start treatment. According to Dendreon Corporation (2012), 75% of patients have minimal or zero out-of-pocket expenses. All Medicare contractors and healthcare plans, which represent 99% of patients with private insurance, cover on-label use of sipuleucel-T (Dendreon Corporation, 2012). Eligible patients are registered for both copayment and travel-expense assistance when needed. Private foundations are accessed through Dendreon-On-Call to provide this support.

Enrollment and Venous Assessment

To start the sipuleucel-T treatment process, the enrollment form is completed and submitted to Dendreon-On-Call. Venous assessment is performed by the APP or infusion nurse for peripheral access with two large bore (16 gauge) IV lines. If a tunneled central venous catheter (CVC) is indicated, arrangements are made for placement of this line and for weekly catheter care to prevent line failure. About 26% of patients in the authors’ institution have required a CVC. Of note, neither a port-a-cath nor a peripherally inserted central catheter provides sufficient venous access (Dendreon Corporation, 2010). The patient is educated about the risks and necessary maintenance of the CVC.

Because Duke University Medical Center is a regional referral center servicing patients from a wide geographic area, care is coordinated with several different leukapheresis centers to minimize travel for patients. Patient availability and preference for location are sent to Dendreon-On-Call to create a detailed written schedule for each patient. This includes dates, times, and addresses for the leukapheresis and infusion centers. Given the complex coordination of transporting and manufacturing the product, the importance of adhering to the schedule must be emphasized to the patient. In addition, the patient is equipped with educational materials provided by Dendreon as well as a practice-designed, detailed information leaflet (see Table 1).

Treatment Process

Leukapheresis

Leukapheresis is the process by which blood is drawn from a vein and leukocytes are selectively separated from red blood
cells, platelets, and plasma, and then reinfused into the patient. This takes place at an independent center, either an American Red Cross or other blood collection center, which is contracted through Dendreon. Prior to the first appointment, the patient’s complete blood count results, history, and leukapheresis order, signed by the prescribing physician, must be sent to the collection center. The complete blood count is required within 30 days of the first leukapheresis procedure to demonstrate that the patient meets the minimum hemoglobin requirements for leukapheresis (usually 10 g/dL).

The collected leukapheresis product is carefully packaged, secured by courier, and transported from the collection site to the airport for delivery to one of the sipuleucel-T manufacturing sites in Atlanta, Georgia, or Orange County, California. Here, detailed processing and quality control steps are completed; the collected mononuclear cells (CD54-positive antigen-presenting cells) are cultured with a fusion protein of PAP and GM-CSF and are allowed to mature and become activated, resulting in personalized sipuleucel-T for infusion. Each dose contains a minimum of 50 million CD54-positive cells. The final sipuleucel-T product is then carefully prepared for delivery to the infusion site. Transportation to and from the manufacturing site is usually via a commercial airline, although other methods of transportation, such as a private driver, are used when necessary to deliver the patient’s sipuleucel-T dose.

**Patient Education Needs**

Patient education for leukapheresis covers several aspects of the procedure. Patients must be prepared to sit still for 3–4 hours with IVs in each arm, or with their CVC accessed, to complete the process. The citrate anticoagulant used in leukapheresis causes hypocalcemia, which may produce a perioral tingling sensation or muscle cramps. This is an anticipated, short-lived reaction that can be minimized with daily oral calcium supplements and increased dietary calcium consumption. If these symptoms develop during the procedure, an over-the-counter antacid made of sucrose and calcium carbonate will be administered. Symptoms resolve quickly in most cases. If necessary, more severely symptomatic patients will receive IV calcium during leukapheresis. The importance of being well-hydrated also is discussed with patients because this makes peripheral veins more accessible and allows the patient to better tolerate the procedure. Patients are encouraged to take their usual medications and to wear loose-fitting clothing to allow access for blood pressure cuff monitoring. These measures increase the potential for treatment success and ensure a more comfortable experience for the patient. Finally, patients should be reassured that leukapheresis does not adversely affect their immune system (Flanigan, Price, Whitmore, & Holman, 2011).

As noted, the leukapheresis procedure generally takes 3–4 hours, after which patients may feel fatigued or weakened; therefore, a friend or family member should be present to accompany them home. However, no restrictions are placed on

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**FIGURE 3. Sipuleucel-T Treatment Delivery Process and Accompanying Patient Education**

- Timing is based on patient’s insurance verification, patient’s schedule, and collection center capacity.
- Generally 4–6 weeks, but shorter if clinically indicated.
- PSA—prostate-specific antigen.
post-leukapheresis activities, and patients are encouraged to continue their usual routines.

**Sipuleucel-T Cellular Infusion**

Three days after cell collection, a private courier collects the final product package from the regional airport and delivers it to the pharmacy at Duke Cancer Center, where it then is transferred to the infusion nurse. The product generally arrives between 10 am and noon, and appointments are scheduled accordingly. On the same morning, a final product disposition notification is faxed to Duke Cancer Center to confirm that the product is acceptable for infusion. Sipuleucel-T arrives in a 250 ml infusion bag within an insulated container inside a cardboard shipping box. Correct storage and handling of the product is paramount (Dendreon Corporation, 2010; Gaines, 2012).

On receipt, the outer cardboard shipping box should be opened to verify the product and patient-specific labels on the insulated container, but the infusion bag must remain within the insulated container until administration; once removed, it cannot be kept at room temperature for more than three hours and cannot be returned to the container. Before administration, the patient’s identity must be confirmed against the details on the infusion bag and the final product disposition notification, and the infusion bag must be inspected for leaks, clumps, and clots. The bag must be rocked gently to disperse any particulates. Infusion must begin before the expiration date and time indicated on the final product disposition notification and the product label. A cell filter must not be used.

Line access (one peripheral IV or CVC) is secured and the patient is premedicated with acetaminophen and diphenhydramine orally 30 minutes before administration to minimize potential infusion reactions. The entire volume of the bag is infused during a period of one hour. The infusion nurse monitors the patient throughout infusion and for 30 minutes after to assess for infusion reactions. In the authors’ practice, most patients tolerate infusion very well; however, among those who do experience infusion reactions, rigors are most common. If a reaction does occur, the infusion is stopped and IV medications such as meperidine and promethazine, or morphine alone, are administered. The infusion is restarted once symptoms resolve. If an infusion reaction does occur, IV formulations of diphenhydramine and famotidine are added as premedications for any subsequent treatments. Other signs and symptoms of infusion reactions were reported during clinical trials and included in the prescribing information. These included fatigue (41%), fever (31%), nausea (22%), headaches (18%), dizziness (12%), muscle aches (12%), difficulty breathing (9%), and high blood pressure (8%) (Dendreon Corporation, 2010). Most reactions are mild to moderate and can be treated in an outpatient setting. Patients with cardiac or pulmonary conditions should be closely monitored for acute infusion reactions, and patients should be encouraged to report any symptoms suggestive of a cardiac arrhythmia (Dendreon Corporation, 2010). Additional information can be obtained via Dendreon Medical Information if a site is actively treating patients or considering doing so.

Three leukapheresis procedures occur, each one followed three days later with infusion of the personalized sipuleucel-T dose. Each couplet is scheduled two weeks apart, although variations of the timing are allowed if necessary. Patients are monitored throughout the treatment phase, with specific visits scheduled prior to the first and third infusions. Notably, throughout this time, patients are continued on their primary androgen-deprivation therapy and bone-targeted agents. If a CVC is in place, the patient must have line care during the non-treatment weeks, including heparin exchange to avoid clotting and dressing change.

**Post-Treatment**

Unless otherwise clinically indicated, patients are scheduled to meet with the primary oncology team about 4–6 weeks after

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**TABLE 1. Patient Education Take-Home Materials**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Key Content</th>
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<tbody>
<tr>
<td>Information leaflet from Duke University Medical Center (prepared by the APP)</td>
<td>• Description of sipuleucel-T and treatment outcomes&lt;br&gt;• Description of and instructions for the leukapheresis process (bring identification, be well-hydrated and eat breakfast, take usual medications, wear loose-fitting clothing, bring a friend or family member)&lt;br&gt;• Description of and instructions for the infusion process (take usual medications)&lt;br&gt;• Possible infusion reactions&lt;br&gt;• Possible special catheter requirements&lt;br&gt;• Possible, but rare, reasons for disruption to the treatment schedule&lt;br&gt;• Getting started: enrollment and being given a treatment schedule&lt;br&gt;• Travel and co-pay assistance&lt;br&gt;• Follow-up&lt;br&gt;• APP contact details</td>
</tr>
<tr>
<td>Schedule letter from Duke University Medical Center (prepared by the APP)</td>
<td>• Treatment schedule and rare disruptions&lt;br&gt;• Address for the leukapheresis center&lt;br&gt;• A reminder of the leukapheresis process and key instructions&lt;br&gt;• A reminder of the infusion process and key instructions&lt;br&gt;• A reminder of possible infusion reactions&lt;br&gt;• PSA level is not a measure of treatment success&lt;br&gt;• APP contact details</td>
</tr>
<tr>
<td>DVD from Dendreon Corporation</td>
<td>• What is sipuleucel-T?&lt;br&gt;• How well does it work?&lt;br&gt;• What are the side effects?&lt;br&gt;• How do I get started?&lt;br&gt;• Am I a good candidate?&lt;br&gt;• What about other treatment options?&lt;br&gt;• Can I afford sipuleucel-T?</td>
</tr>
<tr>
<td>Information leaflets from Dendreon Corporation</td>
<td>• What is sipuleucel-T?&lt;br&gt;• How is sipuleucel-T different?&lt;br&gt;• What are the benefits I might receive from sipuleucel-T?&lt;br&gt;• What important safety information should I know about sipuleucel-T?&lt;br&gt;• How are my cells collected?&lt;br&gt;• How is sipuleucel-T given?&lt;br&gt;• Overview: sipuleucel-T therapy at a glance&lt;br&gt;• What support is available during my treatment?</td>
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</table>

APP—advanced practice provider; PSA—prostate-specific antigen
Ongoing Patient Education

In summary, patient education begins with the primary urology and oncology team and is followed up by the APP who reinforces side effects, benefits, long-term expectations, and next steps. One-to-one patient education is supported by take-home materials, including practice-created and Dendreon publications. The key topics for patient education are summarized in Figure 4.

Maintaining communication with the patient and leukapheresis site throughout the treatment process helps ensure successful delivery of sipuleucel-T therapy. For example, if a concern arises on the morning of a leukapheresis appointment, a discussion can take place in real time to solve the problem and hopefully avoid the need to reschedule the procedure. Patients and their families often have questions throughout treatment; therefore, ongoing re-education and reassurance are important. In particular, patients are used to focusing on PSA as a marker of treatment success or failure. However, for sipuleucel-T, near-term changes in PSA are not reflective of clinical benefit. Therefore, patients need to be oriented to accept PSA increases in this setting.

Conclusion

At Duke University Medical Center, the healthcare team has more than three years of experience using sipuleucel-T and more than 100 patients have been treated. During that time, a multidisciplinary coordinated-care process has been developed to maximize the quality and efficiency of sipuleucel-T delivery. The model ensures a consistent process across many provider teams and facilitates communication with external parties. This multistep process requires coordination among the primary urology and oncology team, the patient, Dendreon, the leukapheresis center, and third-party payors. A primary contact model is used for the coordination of care and patient education, which has proven to provide successful delivery and positive patient experiences during sipuleucel-T treatment. This process is recommended for high-volume centers or for coordinated efforts across multiple practices.

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Implications for Practice

- Develop a multidisciplinary coordinated-care process to identify and evaluate patients for treatment.
- Designate a primary patient contact who is responsible for coordinating care, education, and management. Patient education through preparation for treatment and setting expectations should be central to sipuleucel-T delivery.
- Reassess patients following treatment. Interval history, examination, radiography, and laboratory findings can guide subsequent management.

References


Higano, C.S., Schellhammer, P.F., Small, E.J., Burch, P.A., Nemunaitis,