Practical guide to immunotherapy in castration resistant prostate cancer: the use of sipuleucel-T immunotherapy

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Introduction: New treatment options for metastatic castration resistant prostate cancer (mCRPC) have become available over the last few years should primary treatments and androgen deprivation therapies fail. While historically not considered to be amenable to immunotherapy, the treatment of advanced prostate cancer using this approach is an area of intense interest and now clinical application.
Materials and methods: Recent literature on castration resistant prostate cancer management with a focus on immunotherapeutic strategies was reviewed. Mechanisms of action involving the immunologic treatment of cancer were identified. Agents in clinical trials with near term application in prostate cancer were also identified.
Results: Numerous immunotherapeutic agents for mCRPC are in current clinical trials. The autologous,
active cellular immunotherapy, sipuleucel-T, which utilizes a patient's own antigen-presenting cells, is the only Food and Drug Administration (FDA) approved agent. It provides a 4.1 month survival advantage. Other investigational agents in this area include GVAX, a whole cell irradiated vaccine, and a vaccinia-PSA-TRICOM pox virus based approach, all in phase III trials. Immune-checkpoint inhibitors that enhance T-cell activity and potentiate antitumor effects are also promising.
Conclusions: A first in class novel treatment modality, sipuleucel-T, is available in the United States for mCRPC. Other immunotherapies are in development and may be available in the near future. Understanding the detailed patient evaluation, initiation and administration of sipuleucel-T as described in this paper, will allow this novel cancer immunotherapy to be better understood and potentially benefit a larger group of appropriately selected patients.

Key Words: castration resistant prostate cancer, immunotherapy, sipuleucel-T

Introduction

Prostate cancer is the most common non-cutaneous male cancer and comprises approximately 29% of all newly diagnosed cancer cases in men. While the mortality rate has significantly declined since 1994, arguably due to the introduction of routine prostate-specific antigen (PSA) for early detection and improved therapies of localized disease, at least 29480 prostate cancer related deaths are anticipated in 2014 in the United States.[1] The greatest opportunity for curing prostate cancer occurs when a patient presents with early stage localized disease. Unfortunately, 10%-20% of prostate cancer patients present with metastatic disease, and up to one-third of patients who present at an earlier stage will have disease recurrence despite surgical or radiotherapeutic treatment.[2] In over 80% of men with metastatic disease, primary androgen ablation leads to initial clinical improvement and reduction of serum PSA levels. However, almost all advanced metastatic cancers initially treated with androgen ablation will develop into castration resistant prostate cancer (CRPC), the major cause of morbidity and mortality death in these men.

A significant number of medications have been recently approved for the treatment of CRPC.[3] From 2004 until 2010 only docetaxel was approved for "androgen independent (hormone refractory) metastatic prostate cancer", now referred to as

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metastatic CRPC (mCRPC). Historically, chemotherapy using docetaxel plus prednisone was the only therapy to demonstrate a survival advantage in advanced prostate cancer, making it the "gold standard therapy" in this disease state.

The first of these new drugs approved for mCRPC was an autologous immunotherapy, sipuleucel-T.[4] Since that 2010 approval, there have been other agents with differing modes of action that have demonstrated increased survival in the setting of mCRPC. These include the hormonal agents, abiraterone acetate and enzalutamide, the chemotherapeutic agent cabazitaxel, and bone targeting agents such as the radioactive radium 223 dichloride.[3] These are reviewed in detail elsewhere in this *Canadian Journal of Urology* supplement. This article will focus on immunotherapy in the management of mCRPC.

Principles of cancer immunotherapy

Cancer is considered an immunosuppressive state that requires an intervention to boost adaptive immunity, including the antigen-specific defense mechanism. One of the key characteristics of cancer pathogenesis is the ability of the tumor cell to avoid immune destruction.[5] Mounting evidence has shown that a patient's immune system can be successfully trained to seek out and attack cancer cells by exploiting subtle differences between normal and cancer cells for use as immune recognition targets.[6] Immunotherapeutic approaches to cancer are varied and can be broadly divided into two categories—passive or active.

Passive immunotherapy typically requires direct delivery of cytokines, antibodies, and/or cells of the immune system. Notable success has been achieved in other tumors with exogenously supplied monoclonal antibodies, such as bevacizumab (specific for VEGF), and trastuzumab (specific for HER2/neu) and others which target antigens over-expressed on the surface of solid tumors with anti-tumor efficacy and less toxicity than most chemotherapies.[7] Unconjugated monoclonal antibodies as monotherapy have little or no activity on their own, and agents such as bevicuzimab and trastzumab work best in combination. There also may be the development of antibody dependent cytotoxicty with these agents. PSMA antibodies conjugated to other agents are also under investigation as an immunotherapeutic strategy. Nevertheless, the passive immunotherapeutics which target tumor antigens must be chronically administered and are not self-renewing nor do they appear to provide a sustainable anti-tumor response. Urologic examples include the use of alpha-interferon and IL-2 in the management of renal cell carcinoma.

In contrast, active immunotherapy often referred to as "vaccine therapy" is designed to elicit a host immune response that specifically targets the tumor cell through a T-cell response cascade. Active immunotherapy requires the target antigen to be processed in a manner capable of inducing an immune response that generates anti-tumor activity. T-cells do not respond to soluble or naked protein antigens but rather require peptide fragments from the antigen to be "presented" to them on the surface of antigen-presenting cells (APCs) via human leukocyte antigen (HLA) molecules. Dendritic cells, monocytes, macrophages, and Langerhan cells are all APC that possess the requisite machinery for processing internalized intact protein into peptide fragments which can then stimulate a specific tumor response with memory capabilities.

While a variety of cells can function as APCs, the pivotal steps in the induction of all active T-cell immune responses include the uptake and processing of APCs with antigen and activating the APC to express co-stimulatory molecules and induce cytokine production. APCs are present in substantial quantities in the peripheral blood, and various specialized immune compartments in the body and are the only cells endowed with the ability to stimulate naïve CD4+ T lymphocytes, which can initiate both cellular and humoral immune responses. While the main function of APCs is to internalize and/or process antigen and present antigenic peptides via HLA class I and class II molecules, they also express additional co-stimulatory molecules required for maximal T-cell stimulation. Some of these additional molecules include molecules CD80, CD86, or CD40, as well as intracellular adhesion molecules such as CD54, which are typically upregulated following activation of the APC and serve as marker of APC activation. These co-stimulatory and adhesion molecules signaling events result in T-cell proliferation and cytokine production. Ultimately, the tumor cells are killed through an apoptotic mechanism.[8,9] A common urologic example of active immunotherapy is the use of intravesical BCG for bladder cancer, recognizing that the definitive BCG mechanism of action is unclear.

A newer approach to immunotherapy involves interfering with the immune system's autoregulatory mechanisms, thereby enhancing T-cell activity and potentiating antitumor effects using antibodies targeting immunological checkpoint regulators such as CTLA-4 and PDL-1 that downregulate the immune response pathways.[10]

Prostate cancer as a target for immunotherapy

Training the host immune system to reject its own developing tumor has been a long unrealized dream. A variety of strategies were attempted in the past to stimulate an immune response in the prostate but none proved successful.[11] Based on advances in our understanding of the immune response, prostate cancer has emerged as a good target for exploring immunotherapy for a number of reasons. Mounting evidence suggests that the prostate is predisposed to inflammation, possibly owing to autoimmunity or infection, thus, the host is capable of mounting an immune response against prostate tissue.[12,13] That prostate cancer may be in fact caused by chronic inflammatory mediators adds further to the potential of immunologic therapy of the disease. The slow growth pattern of early prostate cancer also allows time to develop an immune response. Further, the prostate is a highly differentiated, gender-specific organ and prostate adenocarcinoma offers a variety of suitable antigen targets for cancer immunotherapy.[14] Many genes within the prostate are transcriptionally regulated by the androgen receptor and show highly regulated expression mostly restricted to the prostate gland or prostate cancer tissue. Included among such expressed genes are PSA, prostatic acid phosphatase (PAP), prostate-specific membrane antigen (PSMA), and prostate stem-cell antigen (PSCA).

Current leading immunotherapy strategies in prostate cancer

There are a number of investigational strategies under development for the immunotherapy of prostate and other cancers and are beyond the scope of this article. In addition to the approved autologous cellular immunotherapy sipuleucel-T, there are several viable prostate cancer immunotherapy agents that are in late stage clinical trials and have been recently reviewed by Madan and associates.[15]

Therapeutic prostate cancer vaccines
Therapeutic cancer vaccines stimulate immune cells that ultimately target tumor antigens and destroy cancer cells and the toxicity of these approaches appears minimal.

Sipuleucel-T is an example of and ex-vivo processed vaccine for mCRPC. While there are significant up front cost and logistic considerations with this approach, it appears to result in an optimal immune activation and the clinical application of this agent is presented in detail later in this article.

Vector-based vaccines deliver an immune stimulatory message in-vivo to immune cells. One such vaccine, PSA-TRICOM, is currently in phase III testing in mCRPC.[15] PSA-TRICOM consists of two poxviruses administered sequentially without the need for ex-vivo cellular processing. The poxviruses serve as vehicles to transport targeting information to the immune system and trigger an antitumor response. In addition the large poxvirus genome makes them well suited for the insertion of the genes for PSA and 3 T-cell costimulatory molecules that enhance the response.[16] Vaccinia (used in rV-PSA-TRICOM) has a well-established track record of safety in humans as it was used for the successful eradication of smallpox when used as a vaccine. Vaccinia virus has also been administered intravesically in preliminary studies to treat BCG refractory bladder cancer with no significant toxicity.[17] Fowlpox (rF-PSA-TRICOM) serves as the second virus used in this prostate cancer therapeutic combination and is considered safe as it does not replicate in humans.

A non-patient specific allogeneic cellular immunotherapy or whole-cell vaccine approach has been used. GVAX is comprised of two prostate carcinoma cell lines, PC-3 and LNCaP, genetically modified to secrete GM-CSF and radiated before injection. This approach provides multiple potential targets for the immune system. Phase III trials have been disappointing and additional work is needed to optimize this approach.[18]

Immune-checkpoint inhibitors
Immune-checkpoint inhibitors have a unique mechanism of action in cancer. This newly developed class of agents interfere with the immune system's autoregulatory mechanisms.

Anti-CTLA-4 antibodies such as ipilimumab, currently FDA approved for metastatic melanoma, and is currently in phase III testing in in a variety of settings in mCRPC. Blockade of CTLA-4 signaling with ipilimumab prolongs T-cell activation and restores T-cell proliferation, which in turn amplifies T-cell-mediated immunity and the patient's capacity to mount an antitumor response. There is concern over immune-related adverse events (skin, gastrointestinal tract are most frequent) which can be life threatening.[19]

Programmed cell death protein 1 (PD-1) and its ligand (PD-L1) are mediators of immune regulation and are similar to the action of CTLA-4. Anti-PD-1/PDL-1 antibodies are emerging as an alternative to anti-CTLA-4 antibodies. Expression may correlate with better activity of the ligand. It should also be noted that it is not clear whether PD1 or PDL

expression in the tumor or lymphocyte is necessary for an anti-tumor response. The theoretical advantage of targeting the PD-1 axis is less potential toxicity and are in early stage testing in prostate cancer.[20]

Principles of active cellular immunotherapy
One active immunotherapy approach involves APCs that are isolated ex-vivo through leukapheresis and "loaded" with the antigen of choice. This is the principle of sipuleucel-T therapy.[21] Ex-vivo isolation of APC's through leukapheresis and antigen loading provides access to a large number of APCs (10^8 to 10^9 cells). This active cellular immunotherapy offers advantages over passive immunotherapies since the target protein of interest does not have to be restricted to the cell surface. Rather, the target antigen needs only be presented as HLA molecules on cells of the target tissue recognizable by the APC-stimulated T-cells. A sampling of all the proteins produced by a tumor cell are presented as peptide-MHC I class (HLA molecules), which are delivered to the cell surface and are recognized by T-cell receptors of CD8+ T lymphocytes. In favor of autologous active cellular immunotherapy, the ability to access a large number of APCs via the apheresis source has been possible for more than a decade, suggesting that efficient targeting of antigen to these APCs would make the harnessing of the immune system to eradicate tumors tenable. In addition to sipuleucel-T prostate cancer immunotherapy other dendritic cell based therapies are being investigated in many other tumor types using different in-vivo and ex-vivo activation strategies.[22]

An evolving concept in tumor immunology is known as "antigen spreading" that has been observed in the immunotherapy of prostate cancer.[23] This enables the immune system to adapt to tumor mutations and broadens the anti-tumor response. The activated T-cell tumor kill is initially directed against a specific antigen; the release of additional tumor antigens from the lysed cell activates new tumor targeting tumor associated antigens broadening ("spreading") the anti-tumor immune response. Lastly, the concept that immunotherapy works best with lower tumor burdens cannot be underestimated.[24]

Development of sipuleucel-T

Sipuleucel-T represents the first "personalized" immunotherapy for the treatment of cancer using a patient's own immune cells to overcome the self-tolerance hurdle for the treatment of tumors. It is also important to stress that sipuleucel-T is not a gene therapy, since APCs are loaded with a purified recombinant protein and are not genetically manipulated or transfected with any form of viral or recombinant DNA or RNA. The loading of the recombinant protein is performed ex vivo where the optimal concentration of immunogen can be controlled.

PAP was chosen as the target antigen for the prostate cancer treatment because it is expressed at detectable levels in more than 95% of prostate adenocarcinomas and is highly specific to prostate tissue.[25,26] PAP was also reported to be an effective target antigen in experimental models.[27] The receptor for GM-CSF is expressed broadly on blood and bone-marrow derived APCs.[28] Engagement of the GM-CSF receptor by ligand results in the upregulation of the expression of a variety of molecules by APCs, including HLA class II, co-stimulatory molecules noted previously (CD80, CD86, or CD40), adhesion molecules (such as CD54), and a variety of secreted cytokines. Intrinsic to its design, PA2024 (the name of the recombinant fusion protein consisting of GM-CSF and PAP), can bind to the GM-CSF receptor, leading to APC activation, increased expression of adhesion and co-stimulatory molecules, and prolonged APC survival in culture. APC activation results in increased antigen uptake via multiple pathways, most prominently macropinocytosis and receptor-mediated endocytosis. These antigen uptake mechanisms target the internalization of antigen to intracellular compartments linked to HLA class I and class II processing pathways.[29] This approach is designed to be tissue-specificity and to break tolerance to the self-antigen. The final cellular product (APC8015) is suspended in lactated Ringer's and delivered for infusion within 18 hours of suspension.

Clinical evidence for immunotherapy with sipuleucel-T

Two early phase III randomized, double-blind, placebo-controlled trials with sipuleucel-T, (trials D9901 and D9902A) comparing sipuleucel-T to placebo in men with asymptomatic, mCRPC demonstrated significantly prolonged survival.[30] However, these smaller initial trials were combined for an initial FDA filing which led to the need to initiate a larger randomized, double-blind, placebo-controlled Phase III clinical registration trial known as the IMPACT study (Immunotherapy for Prostate AdenoCarcinoma Treatment) (D9902B). These results have been presented previously and led to the approval of sipuleucel-T.[4] Briefly, in the 512 patient IMPACT study, the median OS was 25.8 months for men receiving sipuleucel-T

TABLE 1. **Common adverse events reported in the IMPACT trial (25% or greater incidence)[4]**

Event	Sipuleucel-T (n = 338)		Placebo (n = 168)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any	334 (98.8)	107 (31.7)	162 (96.4)	59 (35.1)
Chills	183 (54.1)	4 (1.2)	21 (12.5)	0
Fatigue	132 (39.1)	4 (1.2)	64 (38.1)	3 (1.8)
Back pain	116 (34.3)	12 (3.6)	61 (36.3)	8 (4.8)
Pyrexia	99 (29.3)	1 (0.3)	23 (13.7)	3 (1.8)
Nausea	95 (28.1)	2 (0.6)	35 (20.8)	0

and 21.7 months for patients who were treated with placebo (p = 0.03), a survival advantage of 4.1 months while possessing a relatively benign safety profile. The IMPACT study randomized patients 2:1 to active treatment versus placebo. Patients who progressed on the placebo arm had the option of participating in a companion study where they could be treated with a reactivated frozen product (APC8015F). A survival advantage was apparent despite the high percentage of subjects (75.6%) randomly assigned to APC-placebo who, following objective disease progression, subsequently received the frozen product. APC8015F was a formulation similar to sipuleucel-T consisting of APCs prepared from cryopreserved APC and loaded with PAP GM-CSF. Adverse events seen more often in sipuleucel-T treated patients than in those receiving placebo included predominantly chills, fatigue, and pyrexia that were Grade 1 or 2 in severity and of short duration (1 or 2 days), resulting in minimal discontinuation of treatment (< 2%), see Table 1.

A highly controversial report using previously unpublished IMPACT trial data has suggested that the increased overall survival in sipuleucel-T-treated men could be an artifact. The authors speculated due to age-related differences in the placebo group (more older men in the placebo group) had a higher chance of dying, because removing white cells was harmful.[31] These highly controversial findings have been definitively refuted by several other authors.[32,33]

As noted, the majority of patients on the placebo arm of the IMPACT study received salvage therapy upon progression with the frozen product. We have previously reported on an analysis of post-progression treatment with APC8015F. This trial design may have actually prolonged survival of subjects in the control arm of sipuleucel-t phase III trials potentially decreasing the absolute overall survival benefit seen with the treatment.[34] This secondary analysis suggested the absolute survival advantage of sipuleucel-T may be up to 10.9 months and possibly longer when the effect of the salvage therapy was considered in the placebo arm.

The use of PSA in the setting of sipuleucel-T requires some clarification. PSA responses may not be observed in patients who have favorable overall survival benefit form sipuleucel-T. In an exploratory analysis of the IMPACT trial, the greatest magnitude of benefit with sipuleucel-T treatment was seen in patients with better baseline prognostic factors, and in particular those with

TABLE 2. **PSA quartile data from the IMPACT study demonstrating improved survival with lower baseline PSA levels[35]**

	Baseline PSA (ng/mL), n = 128			
	≤ 22.1	> 22.1-50.1	> 50.1-134.1	> 134.1
Median OS (months)				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference	13.0	7.1	5.4	2.8
Hazard ratio	0.51	0.74	0.81	0.84
(95% CI)	(0.31, 0.85)	(0.47, 1.17)	(0.52, 1.24)	(0.55, 1.29)

lower baseline PSA values. This suggests that patients with less advanced disease may benefit the most from sipuleucel-T treatment. It provides additional rationale for immunotherapy as an early treatment strategy in sequencing algorithms for mCRPC. PSA quartile data and survival is found in Table 2.[35]

Practical aspects of sipuleucel-T administration

Sipuleucel-T administration can be logistically intensive, requiring a good communication infrastructure between clinicians who perform leukapheresis, the manufacturing facility that performs the ex-vivo procedures on the patient's APCs and prepares the cells for infusion, the patient and the infusion staff. Sipuleucel-T is administered in three treatment cycles and is typically completed in 1 month. Leukapheresis is usually completed early in the week with infusion later in the work week, see Figure 1.

- Each cycle consists of two visits: leukapheresis at an approved cell collection center followed by infusion 3 days later when the product is returned from the processing center
- Each leukapheresis/infusion cycle is generally 1 week
- After the three cycles are completed, no further sipuleucel-T treatments are administered

The manufacturer of sipuleucel-T (Dendreon, Seattle, WA, USA), provides patient and physician scheduling logistical support to insure that the collection, processing and infusion are coordinated. In most cases, insurance company pre-authorization is required. Only manufacturer approved leukapheresis centers can be used for the autologous APC collection. The majority of the information presented below is based on the approved FDA label (available at www.PROVENGE.com; accessed December 15, 2013) and published clinical data.
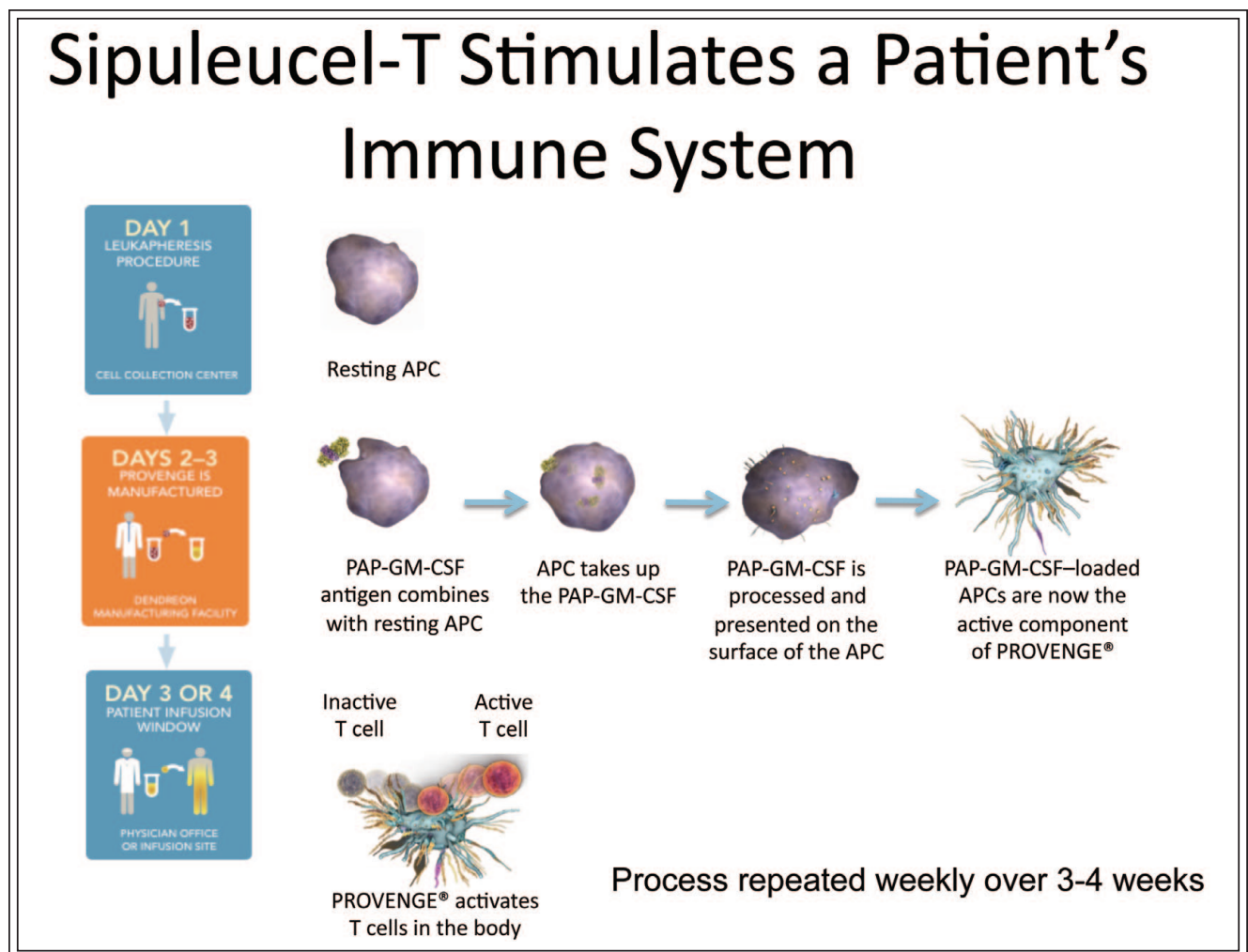

Figure 1. Sequence of sipuleucel-T treatment (Courtesy Dendreon, Seattle, Washington).

The sipuleucel-T FDA label states the formal indication as the "treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer". These men have progressed on traditional androgen deprivation therapy (ADT), such as orchiectomy or gonadotropin-releasing hormone (GnRH) therapies with a confirmed serum testosterone of < 50 ng/dL. The progression is typically defined as a rising PSA with the identification of new or an increased number of metastasis. Imaging men with CRPC should be performed periodically to identify earliest signs if metastasis. The optimum sequence of bone scan and body imaging (CT or MRI) absent symptoms, has not been determined. Na F[18] PET scanning to detect occult bone metastases is understudy and potentially may allow even earlier identification of metastatic disease in this and other settings.

Once metastatic lesions are noted on imaging, men with a castrate level of testosterone and usually a rising are classified as having mCRPC. Over 30% of men thought to have non-metastatic CRPC were found to have metastases when screened via imaging on a recent clinical trial.[36] However, the patient should be asymptomatic or minimally symptomatic and not require narcotic medications for cancer-related pain. According to the NCCN Guidelines (Prostate Cancer Version 1.2014, accessed December 16, 2013) sipuleucel-T is appropriate for patients with ECOG performance status 0-1 and should not be used in patient with hepatic metastasis or with a life expectancy of < 6 months. It is also listed as second line therapy for mCRPC. There are no formally noted contraindications for the sipuleucel-T therapy on the FDA label.

A CBC should be obtained 1 month before the first treatment cycle to ensure adequate hematologic parameters to undergo leukapheresis. In order to insure adequate access for leukapheresis, a "venous assessment" at least 1 week before the first cycle is required to determine whether placement of a formal apheresis catheter is needed. Peripheral IV's are the preferred method of leukapheresis collection; verify access in both arms since leukapheresis is a dual-arm procedure. However, some patients with inadequate peripheral access may require an apheresis catheter. Twenty three percent of patients in sipuleucel-T clinical trials required an apheresis catheter.[37] Apheresis catheters that provide central venous access are commonly placed by interventional radiology. Peripherally inserted central catheter (PICC) lines are usually not considered appropriate.

Patients should be informed about the nature of the leukapheresis procedure. It can last 3-4 hours and patient should be well hydrated, avoid caffeinated beverages on the day of the procedure and eat a calcium rich breakfast. Loose fitting clothing is encouraged. Side effects of the leukapheresis procedure can include perioral and digital tingling, sensation of chills, nausea and fainting. Photo ID is essential so that proper sample identification is insured at all steps in the treatment cycle. The patient should be accompanied by an adult as the procedure can cause some fatigue.

The leukapheresis product is then shipped to the Dendreon processing facility where it is treated ex-vivo with a recombinant fusion protein, PA2024 (human PAP fused GM-CSF). The activated autologous product, now officially called sipuleucel-T is usually returned within 48-72 hours to the infusion site. It contains a minimum of 50 million autologous CD54+ cells activated with PAP GM-CSF, suspended in 250 mL of lactated ringers in a sealed, patient-specific infusion bag. It should be stored refrigerated at 2°C-8°C and not frozen.

In order to minimize infusion reactions, it is recommended that patients be premedicated with 650 mg of acetaminophen and an antihistamine such as 50 mg diphenhydramine 30 minutes before. Patient identity must be verified by photo ID. After fax or e-mail confirmation from the manufacturer that the product is "approved for infusion", (post-manufacture product quality assurance and expiration date and time) it is infused through a peripheral IV (18-20 gauge needle preferred) or appropriately prepared apheresis catheter (if present). It is critical that no in-line filter or blood component infusion tubing be used in the infusion set up. Normal saline is the IV solution of choice. The product should remain in the insulated shipping container with the lid in place until the patient is ready to receive the infusion. Universal precautions should be used when handling sipuleucel-T because as an autologous product, it is not routinely tested for transmissible infectious diseases and may carry the risk of transmitting infectious diseases to health care professionals handling the product.

Post-manufacture product quality assurance verifies that the minimum requirements of activated CD54+ cell are present by measuring the increased expression of the CD54 (also known as ICAM-1), on the surface of APCs after culture with the PAP GM-CSF. The product is also approved for infusion based on the microbial and sterility results from several tests: contamination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion and will be reported to the physician with any follow up as needed.

The product should be infused over 60 minutes. Interrupt or slow infusion for acute infusion reactions, depending on the severity of the reaction. The most common adverse reactions are noted in Table 1. In controlled clinical trials, symptoms of acute infusion reactions were treated with acetaminophen, IV histamine (H1 and/or H2 blockers), and low dose IV meperidine. Do not resume the infusion if the sipuleucel-T has been held at room temperature for greater than 3 hours. The patient should be observed for 30 minutes after infusion for any adverse reactions.

This entire procedure is repeated for three cycles. If, for any reason, the patient is unable to receive a scheduled infusion, the patient will need to undergo an additional leukapheresis if the course of treatment is to be continued. Patients should be advised of this possibility prior to initiating treatment.

Sipuleucel-T treatment follow up

Routine mCRPC follow up care is indicated after sipuleucel-T therapy. Patients and clinicians should be made aware that PSA may not be used as a definitive marker for response following immunotherapy. As noted previously, PSA provides guidance concerning the men who might be optimum candidates for immunotherapy with sipuleucel-T but is not a reliable marker of response. There is no consensus as to when patient should be reimaged, and that the median time to second treatment on the IMPACT study was 6 months driven primarily by imaging studies.

Immunotherapy generally has the most benefit with early and lower tumor burden. The dynamics of immunotherapy are distinct from cytotoxic chemotherapy whereby the tumor growth rate may be significantly slowed resulting in extended survival but this can be difficult to determine in the course of routine clinical care.[38,39]

There is a pressing need to identify predictive biomarkers in the setting of immunotherapy. Recently, Sheikh et al analyzed immunological responses and overall survival through the assessment of antigen-specific cellular and humoral responses in a subset of men enrolled in the IMPACT study.[40] APC activation based on CD54 occurred in the first dose was increased with the second and third dose preparations; this increase correlated with overall survival. Interferon gamma (IFNγ) enzyme-linked immunosorbent spots (ELISPOT) also correlated with overall survival. This preliminary data provides insight on which patients may benefit from improved overall survival through induction of antigen-specific immune activation and also provides direction for future biomarker research.

Conclusions

Improved understanding of the interactions between the immune system and prostate cancer has generated renewed interest in treating prostate cancer with immunotherapy. While there are several promising immunotherapeutic agents under study, sipuleucel-T is clinically available as the first in class antigen-specific autologous immunotherapy approved for cancer treatment. Combining sipuleucel-T with other agents and further study of the optimum sequencing of immunotherapy will continue for the next few years.[41] Understanding the basic principles behind prostate cancer immunotherapy and the optimum clinical application of sipuleucel-T will potentially benefit many men with minimally symptomatic or asymptomatic metastatic castration-resistant prostate cancer.

Disclosure

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