An Analysis of Leukapheresis and Central Venous Catheter Use in the Randomized, Placebo Controlled, Phase 3 IMPACT Trial of Sipuleucel-T for Metastatic Castrate Resistant Prostate Cancer

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Purpose: Sipuleucel-T is an autologous cellular immunotherapy. We review the safety of the leukapheresis procedure required for sipuleucel-T preparation and complications related to venous catheter use in the randomized, placebo controlled phase 3 IMPACT (IMmunotherapy for ProstAte Cancer Trial) study (NCT 00065442).

Materials and Methods: A total of 512 patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer were enrolled in the study. All patients were scheduled to undergo 3 standard 1.5 to 2.0 blood volume leukapheresis procedures at 2-week intervals. Leukapheresis related adverse events and those related to venous catheter use were reviewed. Immune cell counts were examined throughout the treatment course.

Results: Of 512 enrolled patients 506 underwent 1 or more leukapheresis procedures and were included in this analysis. Adverse events were comparable between the sipuleucel-T and control arms. Leukapheresis related adverse events were primarily associated with transient hypocalcemia (39.3%). Most leukapheresis related adverse events (97%) were of mild/moderate intensity. Median white blood cell count and absolute monocyte and lymphocyte counts were stable and within normal ranges throughout the treatment course. Of all patients 23.3% had a central venous catheter placed primarily for leukapheresis. Patients with vs without a central venous catheter had a higher risk of infection potentially related to catheter use (11.9% vs 1.3%, $p < 0.0001$) and a trend toward a higher incidence of venous vascular events potentially related to catheter use, excluding the central nervous system (5.9% vs 2.1%, $p = 0.06$).

Conclusions: Adverse events related to leukapheresis are manageable and quickly reversible. The majority of patients can undergo leukapheresis without a central venous catheter. Central venous catheters are associated with an increased risk of infections and venous vascular events. Peripheral intravenous access should be used when feasible.

Key Words: prostatic neoplasms, immunotherapy, sipuleucel-T, leukapheresis, catheters

Abbreviations and Acronyms

AE = adverse event

APC = antigen presenting cell

CVC = central venous catheter

GM-CSF = granulocyte-macrophage colony-stimulating factor

IV = intravenous

mCRPC = metastatic castrate resistant prostate cancer

PAP = prostatic acid phosphatase

PBMC = peripheral blood mononuclear cell

WBC = white blood cell

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PROSTATE cancer is the second leading cause of cancer death among American men and will account for an estimated 28,000 deaths in the United States in 2012.[1] Although fewer than 5% of patients with prostate cancer present with metastases, up to 30% of those treated for clinically localized

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disease experience recurrence.[2] Androgen deprivation therapy is an effective first line treatment for patients with advanced disease, but the cancer often progresses to a castrate resistant state after 12 to 24 months.[3]

Sipuleucel-T is an autologous cellular immunotherapy which was approved by the United States Food and Drug Administration in 2010 for asymptomatic or minimally symptomatic mCRPC. It is prepared by culturing the patient's PBMCs, obtained via leukapheresis, with a recombinant antigen consisting of PAP linked to GM-CSF. The product, including activated APCs expressing PAP-GM-CSF epitopes on their surface, is then reinfused into the patient to stimulate an immune response against prostate cancer. In the phase 3 IMPACT trial (NCT 00065442), a randomized, placebo controlled trial of 512 patients, sipuleucel-T was associated with a 22% relative risk reduction of death (HR 0.78, 95% CI 0.61–0.98, p = 0.03) and a prolongation of median overall survival by 4.1 months.[4]

Leukapheresis, an essential step in the preparation of sipuleucel-T, is performed at a qualified regional apheresis center. The procedure requires the administration of an anticoagulant to minimize the risk of blood clotting ex vivo. The most commonly used anticoagulant during leukapheresis is citrate due to its short half-life and favorable safety profile. Citrate works as an anticoagulant by binding calcium, an important factor in the coagulation and platelet aggregation cascades,[5] and can lead to transient hypocalcemia. Thus, it is common for patients undergoing leukapheresis to experience symptoms of mild hypocalcemia including paresthesias, nausea and lightheadedness (ie citrate toxicity).[6]

While the leukapheresis procedure and infusion of sipuleucel-T can be accomplished with standard peripheral IV access in the majority of patients, some may require a central venous catheter. CVCs have certain advantages such as a ready source of access, consistent blood flow during the leukapheresis procedure and no need for repeated peripheral venipunctures. However, they are also associated with complications including infections, occlusion and thromboses. Furthermore, the risk of complications increases with the duration of the indwelling CVC.[7] In this study we report the safety of the leukapheresis procedure required to collect PBMCs and the complications associated with CVC use in the IMPACT trial.

METHODS

Patients

The study design and results of the phase 3 IMPACT trial were previously reported.[4] Eligible patients had asymptomatic or minimally symptomatic mCRPC with an ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0 or 1 and castrate testosterone levels (less than 50 ng/dl). Those who had been treated with 2 or fewer chemotherapy regimens or who were on bisphosphonate therapy were eligible for study inclusion. Eligibility criteria also included hemoglobin 9 gm/dl or greater, WBCs 2,000/μl or greater and a platelet count of 100,000/μl or greater. Exclusion criteria were visceral metastases, long bone fractures, spinal cord compression and treatment within the previous 28 days with systemic glucocorticoids, external beam radiation, surgery or systemic therapy for prostate cancer other than castration. The study was approved by the institutional review board at each study center. All patients provided written informed consent.

Randomization and Treatment

Between 2003 and 2007 a total of 512 patients were enrolled in IMPACT, and were randomized in a 2:1 ratio to receive sipuleucel-T (341) or control (nonactivated, autologous PBMCs, 171) every 2 weeks for a total of 3 infusions. Sipuleucel-T and the control intervention were prepared as previously described.[4,8,9] The course of therapy is outlined in figure 1. Standard leukapheresis preceded infusions of sipuleucel-T or control by approximately 3 days. Leukapheresis typically lasted 2 to 4 hours, during which 1.5 to 2.0 times the patient's total blood volume was processed. If a product could not be prepared or did not meet release specifications, patients could undergo additional leukaphereses to allow 3 infusions to be received. IV or oral calcium could be administered before or during the leukapheresis procedure to prevent or treat citrate toxicity according to local apheresis center policy.

Sipuleucel-T and control infusions were prepared at a central manufacturing facility. During sipuleucel-T preparation, APCs were cultured with media containing the PAP-GM-CSF fusion protein for 36 to 44 hours. The control was prepared by culturing APCs in medium without the protein. Infusions of sipuleucel-T and control were administered during a period of approximately 60 minutes after premedication with acetaminophen and an antihistamine. A peripheral intravenous catheter or a CVC could be used for the leukaphereses and infusions. Bilateral peripheral IV access with a 17 to 20 gauge needle was required for leukapheresis and an 18 to 22 gauge catheter was required for infusion.

Adverse Events

The safety population was defined as all patients who underwent at least 1 leukapheresis procedure. AEs related to leukapheresis were defined as those events occurring within 24 hours of the procedure. Adverse infectious and nonneurological vascular complications potentially related to venous catheter use were defined as those events occurring from the date of first leukapheresis until 30 days after the last infusion or leukapheresis (whichever occurred later) and having a coded/verbatim term possibly consistent with a catheter etiology. AEs were graded using the National Cancer Institute Common Terminology Criteria for AEs, version 3.0, and coded with MedDRA (Medical Dictionary for Regulatory Activities) version 11.0 preferred terms. No formal statistical testing for AEs was planned for the trial.[10] Comparisons of categorical variables between groups of patients were made using Fisher's