Quality of Life After Sipuleucel-T Therapy: Results From a Randomized, Double-blind Study in Patients With Androgen-dependent Prostate Cancer

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OBJECTIVE To collect and analyze quality-of-life (QOL) data from PROvenge Treatment and Early Cancer Treatment trial (PROTECT, NCT00779402), a phase III, randomized controlled trial of sipuleucel-T in patients with asymptomatic androgen-dependent prostate cancer.

METHODS Patients experiencing prostate-specific antigen relapse after radical prostatectomy entered a 3- to 4-month run-in phase of androgen-deprivation therapy (ADT), followed by 2:1 randomization to sipuleucel-T or control. QOL was assessed throughout the run-in and 26-week post-randomization phases using the Brief Fatigue Inventory (BFI), Linear Analog Self-Assessment (LASA) scale, Global Rating of Change (GRoC) scale, and an elicited symptoms list.

RESULTS One hundred seventy-six patients were randomized into 2 groups, the sipuleucel-T group (n = 117) or the control group (n = 59). The sample provided 80% power to detect a difference in fatigue interference score between treatment arms of 0.9 points. QOL declined predictably during ADT. At week 26, 26.2% of sipuleucel-T-treated patients and 21.6% of control-treated patients ($P = .68$) reported fatigue in the previous week, and the mean score for fatigue interference in the past 24 hours was 0.9 for both arms ($P = .88$). Results were comparable for usual fatigue ($P = .91$) and worst fatigue ($P > .99$). Mean LASA scores decreased in both groups ($P = .26$). The proportion of patients reporting better overall QOL on GRoC was similar ($P = .62$).

CONCLUSION There is no clinically significant negative impact on QOL after sipuleucel-T treatment compared with control after a period of ADT in patients with asymptomatic androgen-dependent prostate cancer. UROLOGY 82: 410–415, 2013. © 2013 Elsevier Inc.

Immunotherapy has an established role in the management of urologic cancers, modulating disease in localized bladder cancer, and advanced kidney cancer. More recently, the autologous cellular immunotherapy sipuleucel-T (Provenge; Dendreon Corporation, Seattle, WA) has been shown to prolong survival in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), with a median survival advantage of 4.1 months compared with control.[1] Sipuleucel-T consists of a patient's peripheral blood mononuclear cells activated ex vivo with a recombinant protein containing prostate tumor antigen prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor.

Androgen-deprivation therapy (ADT) and conventional chemotherapy for prostate cancer are associated with substantial toxicity and can adversely affect quality of life (QOL).[2-7] In contrast, sipuleucel-T is associated with limited toxicity[1,8,9] and, thus, has the potential to preserve QOL. However, QOL assessments were not included in the sipuleucel-T pivotal trials.

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The PROvenge Treatment and Early Cancer Treatment trial (PROTECT, P-11, NCT00779402),[10] which evaluated sipuleucel-T vs control after a 3- to 4-month course of ADT in patients with rising prostate-specific antigen (PSA) after radical prostatectomy, offered the first opportunity to assess QOL after sipuleucel-T. The primary analysis demonstrated no association between sipuleucel-T and time to biochemical failure, defined as PSA $\geq$3 ng/mL (median time to biochemical failure: 18.0 months with sipuleucel-T vs 15.4 months with control, $P = .737$). However, after testosterone recovery, there was a 48% increase in PSA doubling time with sipuleucel-T ($P = .038$). Sipuleucel-T was well tolerated, with an adverse-event (AE) profile similar to the control group.

QOL data were collected in PROTECT and the primary objective of this analysis was to compare QOL assessed via several instruments after sipuleucel-T or control treatment. As patients had asymptomatic androgen-dependent prostate cancer (ADPC), any confounding effects of the disease process on QOL were avoided.

MATERIAL AND METHODS

Study Design

PROTECT was a randomized, double-blind, controlled trial in patients with nonmetastatic ADPC performed at 17 centers across the United States.[10] It enrolled men aged 18-80 years who had undergone radical prostatectomy for histologically confirmed prostate cancer 3 months to 10 years previously and whose only sign of disease recurrence was a rise in serum PSA. Eligible patients had Eastern Cooperative Oncology Group performance status 0 or 1, life expectancy $\geq$1 year, tumor positive for prostatic acid phosphatase by immunohistochemistry, and serum PSA nadir after radical prostatectomy <0.4 ng/mL. Patients experiencing a first PSA relapse within 2 years of radical prostatectomy were eligible regardless of Gleason score, whereas only patients with Gleason score $\geq$7 were eligible if first PSA relapse occurred between 2 and 10 years post-radical prostatectomy. Patients who had received adjuvant or salvage radiation, or luteinizing hormone-releasing hormone analog (LHRH-a) or nonsteroidal antiandrogen therapy for a previous PSA relapse, were eligible if PSA did not rise during hormonal therapy and 6 months had elapsed since the last effective date of treatment. Exclusion criteria included metastatic disease, PSA $\geq$20 ng/mL any time after prostatectomy, orchiectomy, and prior immunotherapy.

Patients initially received ADT with a 3-month LHRH-a depot. Patients with PSA <1 ng/mL were then randomized 2:1 to sipuleucel-T or control, with no further ADT. Patients with PSA $\geq$1 ng/mL received an additional 1-month LHRH-a depot and were eligible for randomization if PSA subsequently declined to <1 ng/mL. All patients provided written informed consent and the trial protocol received local institutional review board approval.

Randomized treatment was administered at weeks 0, 2, and 4. Before treatment initiation, patients underwent a 1.5-2.0 blood volume mononuclear cell leukapheresis. Patients were infused 2 or 3 days after leukapheresis with sipuleucel-T or control (peripheral blood mononuclear cells without addition of prostatic acid phosphatase-granulocyte-macrophage colony-stimulating factor).[1]

QOL Instruments

With week 0 denoting the first week of immunotherapy, QOL assessments were made at weeks -1, 13, and 26, and at one or both visits during the ADT run-in period (week -13 and/or -7). Four instruments were used: Brief Fatigue Inventory (BFI),[11] Linear Analog Self-Assessment (LASA) scale,[12] Global Rating of Change (GRoC) scale,[13] and a predefined elicited symptoms checklist.

On BFI, patients were asked whether they had experienced unusual fatigue or tiredness in the past week. Patients answering "yes" rated their usual and worst fatigue in the past 24 hours (0 = no fatigue, 10 = as bad as one can imagine) and how fatigue had interfered (0 = does not interfere, 10 = completely interferes) with 6 aspects of their lives (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life). Patients answering "no" were assigned a score of 0 for all missing fatigue items. Using LASA, patients ranked their perceived state of health from 0 to 100, the latter being the most desirable health state. GRoC categorized the change in QOL ("same," "worse," or "better"). The defined elicited symptoms were hot flashes/sweats, loss of muscle strength, memory loss/absent-mindedness, bone/joint pain, breast tenderness/pain, breast enlargement, gastrointestinal disturbance or abnormal bowel movements, reduced sexual desire, and reduced sexual function.

Statistical Analyses

For BFI and LASA measurements, mean (SE) and median values were calculated at each time point, and for the change from week -1. The *t* test was used to compare mean values and changes from week -1 in the 2 groups at weeks 13 and 26. The Fisher exact test compared the incidence of fatigue and each elicited symptom between treatment groups. The Cochran-Mantel-Haenszel row mean scores test compared the GRoC ratings for the treatment groups at weeks 13 and 26 vs week -1, and at week -1 vs week -13. In all summaries and analyses, no imputation for missing QOL data was performed. All reported *P* values are 2-tailed with no adjustment for multiplicity.

The sample size in PROTECT was based on the primary endpoint: time to biochemical failure. To facilitate interpretation of the QOL results, post hoc power calculations were made. Based on the observed data for change in fatigue interference score from week -1 to 26, the sample provides 80% power at the 2-sided, 0.05 significance threshold to detect a difference between treatment arms of 0.9 points (scale of 0-10). This calculation is based on an evaluable sample size of 144 patients randomized in a 2:1 ratio and assuming a common SD of 1.8.

RESULTS

Patient Characteristics and Disposition

The PROTECT trial enrolled 208 patients, of whom 176 were randomized (sipuleucel-T, n = 117; control, n = 59) (Fig. 1). All patients except 1 underwent at least 1 leukapheresis procedure. As reported in the primary publication of this trial,[10] patient demographic and baseline characteristics appeared evenly balanced between treatment arms. Median patient age was 64 and 67 years in the sipuleucel-T and control groups, respectively. Eastern Cooperative Oncology Group performance status was 0 for 94.8% and 98.3% of patients, respectively. Only a minority of patients, 17.9% and 15.3%,