Lower Baseline PSA Predicts Greater Benefit From Sipuleucel-T

Schelhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology*. 2013 Apr 9. pii: S0090-4295(13)00225-2. doi: 10.1016/j.urology.2013.01.061. [Epub ahead of print]

Background

Sipuleucel-T (Provenge, Dendreon) is an autologous cellular immunotherapy that is approved by the US Food and Drug Administration for use in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). It was designed to stimulate antitumor activity by inducing an immune response against prostatic acid phosphatase, an enzyme present in most prostate cancers.

Sipuleucel-T is produced by co-culturing freshly isolated peripheral blood mononuclear cells (PBMCs) with PA2024, a recombinant protein consisting of prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor (GM-CSF). PBMCs that have been cultured with PA2024 form the sipuleucel-T product. Sipuleucel-T is administered via an intravenous infusion, which is given over a total of 3 infusions spaced approximately 2 weeks apart. A new sipuleucel-T product must be produced from each patient for each infusion. Thus, PBMCs are obtained via leukapheresis on weeks 0, 2, and 4 of sipuleucel-T therapy.

The efficacy and safety of sipuleucel-T in patients with mCRPC were evaluated in the randomized, controlled, double-blind, phase III IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial, which enrolled 512 patients with mCRPC.[1] The median age of enrolled patients was 71 years; 82% were chemotherapy-naïve. The study was initially open only to patients with asymptomatic disease, a Gleason score of 7 or less, and a prostate-specific antigen (PSA) level of 5 ng/mL or greater. However, the protocol was amended to include patients with any Gleason score and those with minimally symptomatic disease. Exclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater, visceral metastases, and previous treatment with 3 or more chemotherapy regimens.

In the trial, all patients underwent leukapheresis at weeks 0, 2, and 4. Patients were randomly assigned to receive 3 infusions of either sipuleucel-T or a control treatment consisting of PBMCs that had been cultured without PA2024. Each treatment was administered throughout a 60-minute intravenous infusion given approximately 3 days after each leukapheresis. Upon disease progression, patients in the control arm could enter into an open-label salvage trial evaluating a treatment based on the same protocol as sipuleucel-T, but which used PBMCs that were cryopreserved during the initial preparation of control cells (a treatment called APC8015F).

Table 1. Baseline Factors Prognostic for Survival in a Multivariate Analysis of the IMPACT Trial

Variable	Hazard Ratio	95% Confidence Interval	*P*-Value
PSA (log-transformed)	1.220	1.123–1.325	<.0001
LDH (log-transformed)	2.208	1.438–3.393	.0003
Hemoglobin	0.861	0.790–0.939	.0007
ECOG PS of 1 (vs 0)	1.525	1.154–2.015	.0030
ALP (log-transformed)	1.250	1.035–1.510	.0206

ALP=serum alkaline phosphatase; ECOG PS=Eastern Cooperative Oncology Group performance status; IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment; LDH=serum lactate dehydrogenase; PSA=prostate-specific antigen.

Data from Schelhammer PF et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology*. 2013 Apr 9. pii: S0090-4295(13)00225-2. doi: 10.1016/j.urology.2013.01.061. [Epub ahead of print][3]

Table 2. Baseline Characteristics and Subsequent Treatments According to Baseline PSA Quartile in the IMPACT Trial

Parameter	Baseline PSA (ng/mL)			
	≤22.1 ng/mL (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Baseline Characteristic				
Median age, years (range)	70 (45–88)	70 (50–89)	73 (42–89)	73 (40–91)
Median weight, lbs (range)	201 (139–384)	190 (116–350)	191 (131–320)	188 (121–312)
>10 bone metastases, %	19.5	33.6	53.1	64.8
ECOG PS=1, %	12.5	13.3	21.1	25.8
Gleason score ≤7, %	81.3	71.9	74.2	74.8
Prior docetaxel, %	6.3	10.9	11.7	28.9
Median ALP, U/L (range)	89.5 (42–585)	93.5 (18–506)	116.0 (47–1,443)	137.5 (51–2,813)
Median hemoglobin, g/dL (range)	13.2 (9.4–16.2)	13.1 (8.4–15.6)	12.7 (9.1–17.9)	12.0 (9–15.4)
Median LDH, U/L (range)	184.5 (84–301)	193.0 (135–407)	200.0 (101–1,662)	203.5 (129–654)
Subsequent Treatment				
Docetaxel, %	59.4	57.0	53.1	50.0
APC8015F salvage control group, %	73.3	75.6	59.1	43.2

ALP=serum alkaline phosphatase; ECOG PS=Eastern Cooperative Oncology Group performance status; IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment; LDH=serum lactate dehydrogenase; PSA=prostate-specific antigen.

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In the primary analysis of IMPACT, published in the *New England Journal of Medicine* in 2010, sipuleucel-T was associated with a 22.5% reduction in the risk of death compared with the control treatment (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.61–0.98; *P*=.03).[1] The median overall survival was 25.8 months in the sipuleucel-T arm and 21.7 months in the control arm, indicating a median survival improvement of 4.1 months. Estimated 3-year survival rates were 31.7% and 23.0%, respectively.

To determine the benefit of sipuleucel-T in different patient populations, subgroup analyses were performed based on 19 baseline characteristics that have been shown to predict survival and stratify patients in randomized phase III trials.[2] These include serum lactate dehydrogenase (LDH), PSA, serum alkaline phosphatase (ALP), Gleason score, ECOG performance status, and hemoglobin level. Although presence of visceral disease is among the previously identified independent prognostic factors, the IMPACT trial excluded patients with visceral disease, and thus the benefit of sipuleucel-T in patients with visceral disease was not evaluated.

Subgroup analyses showed a consistent benefit with sipuleucel-T across all evaluated subgroups. One factor that did appear to predict a relatively greater benefit of sipuleucel-T was baseline PSA; there was a trend toward greater survival improvement with sipuleucel-T among patients with a baseline PSA at or below the median (HR for sipuleucel-T vs control: 0.685) compared with those with a baseline PSA above the median (HR for sipuleucel-T vs control: 0.865). These findings suggested that sipuleucel-T may have a particular benefit for patients with a lower disease burden.

Study Design

The current analysis was undertaken to further evaluate the prognostic and predictive values of these variables that are known to be associated with survival in patients with mCRPC.[3] Because the binary classification according to baseline PSA (at or below median vs above median) showed a difference in sipuleucel-T benefit, patients were further categorized according to baseline PSA quartile. Other evaluated subsets included ECOG performance status (0 vs 1), Gleason score (≤7 vs ≥8),

Table 3. Survival Outcomes by PSA Quartile in the IMPACT Trial

Parameter	Baseline PSA (ng/mL)			
	≤22.1 ng/mL (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference between groups, months	13.0	7.0	5.4	2.8
Hazard ratio (95% CI)	0.51 (0.31–0.85)	0.74 (0.47–1.17)	0.81 (0.52–1.24)	0.84 (0.55–1.29)

CI=confidence interval; OS, overall survival; PSA=prostate-specific antigen.

Data from Schelhammer PF et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology*. 2013 Apr 9. pii: S0090-4295(13)00225-2. doi: 10.1016/j.urology.2013.01.061. [Epub ahead of print][3]

mean LDH, median ALP, and median hemoglobin. The prognostic value of each factor was assessed using Cox regression models. Sensitivity analyses were also performed for baseline PSA and LDH.

In a stepwise multivariate Cox regression analysis of the IMPACT trial, the factors that were significantly prognostic for survival across treatment arms included PSA, LDH, hemoglobin, ECOG performance status, and ALP (P<.05; Table 1). The only evaluated variable not significantly associated with survival was Gleason score.

The survival benefit observed with sipuleucel-T appeared to be consistent across all evaluated subgroups. There was no significant treatment interaction between sipuleucel-T and any single characteristic. However, several baseline characteristics associated with a more favorable prognosis were also associated with a relatively greater benefit of sipuleucel-T. These characteristics included PSA at or below the median (vs above the median), LDH at or below the median (vs above the median), and ECOG performance status of 0 (vs 1).

Although ALP was not predictive of a greater benefit with sipuleucel-T in the overall analysis, there was a relatively greater treatment effect with sipuleucel-T among the 48% of patients (n=247) with bone-only disease. Within this subgroup, there appeared to be a trend toward greater benefit with sipuleucel-T among patients with a lower baseline ALP (defined as ≤103 U/L) compared with a higher baseline ALP (defined as >103 U/L), with HRs for survival with sipuleucel-T versus control of 0.592 (95% CI, 0.329–1.064) and 0.776 (95% CI, 0.488–1.235), respectively.

In most cases, the more favorable prognostic factor was associated with a relatively greater benefit from sipuleucel-T, but there were exceptions. Whereas a higher hemoglobin level was associated with a more favorable prognosis, the benefit from sipuleucel-T appeared to be greater in patients with lower hemoglobin levels (at or below the median) than in patients with hemoglobin levels above the median.[1]

A more detailed analysis of the prognostic and predictive value of baseline PSA by quartile in the IMPACT trial showed a significant association between baseline PSA and other favorable prognostic features, including ALP, ECOG performance status, and use of subsequent therapies (Table 2). Notably, an analysis of baseline characteristics and use of subsequent therapies showed no significant difference between treatment arms overall or by PSA quartile.

An analysis of survival in the IMPACT trial according to baseline PSA showed a reduction in survival with each decreasing PSA quartile in both the sipuleucel-T and control groups. The HR for survival with sipuleucel-T versus control also decreased with increasing PSA quartile, indicating that the greatest benefit from sipuleucel-T was observed among patients in the lowest PSA quartile group (Table 3). Among those 128 patients, sipuleucel-T was associated with a 49% reduction in the risk of death versus the control treatment (HR, 0.51; 95% CI, 0.31–0.85) and a 50% relative improvement in the estimated 3-year survival rate (62.2% vs 41.6%).

Clinical Relevance

Previous analyses from the IMPACT trial demonstrated a benefit with sipuleucel-T in multiple subgroups of patients with mCRPC. This exploratory analysis provided further information on the relative benefit of sipuleucel-T according to baseline characteristics. There was a trend toward a relatively greater benefit with sipuleucel-T among patients with more favorable baseline prognostic factors, particularly in patients with a low baseline PSA level, in whom sipuleucel-T was associated

with a 49% reduction in the risk of death compared with the control treatment.

Other prognostic factors associated with a greater benefit from sipuleucel-T included lower LDH, better performance status, and, among patients with bone-only disease, lower baseline ALP.

The authors suggested that the enhanced benefit of sipuleucel-T among patients with more favorable prognostic factors may relate to the proposed mechanism of action of the agent. Sipuleucel-T is thought to work by inducing an antitumor immune response. If that is the case, the effectiveness of the therapy would be influenced by the immune system's ability to mount an effective immune response. It has been reported that a higher tumor burden is associated with greater immunosuppression.[4,5] Thus, patients with more advanced disease may be less able to generate a strong antitumor immune response. Indeed, data indicate that patients with earlier stage disease exhibit greater antigen-presenting cell activation during sipuleucel-T production than patients with more advanced disease.[6] Phase III trials have demonstrated an association between extent of antigen presentation cell activation and overall survival.[6]

The second proposed explanation for the observation of greater benefit of sipuleucel-T among patients with earlier disease relates to the time required for sipuleucel-T to induce an immune response. If sipuleucel-T is administered earlier in the course of the disease, this allows more time for the generation of a sustained immune response and more time for patients to benefit from the treatment.

This trend differs from those associated with other agents used in mCRPC, including docetaxel,[7] abiraterone acetate (Zytiga, Janssen Biotech),[8] and enzalutamide (Xtandi, Astellas Pharma),[9] in which a greater treatment effect has been demonstrated among patients with higher baseline PSA, and cabazitaxel (Jevtana, sanofi-aventis), which showed a greater effect in patients with a rising PSA.[10] These findings suggest that immunotherapy may be more effectively used in earlier-stage disease, when there is a lower disease burden, whereas cytoreductive therapy may be more appropriate in patients with a higher disease burden.

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Commentary

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Since 2010, 5 new drugs have been approved for the treatment of castration-resistant prostate cancer. Classes of agents include: 1) immunotherapy, 2) chemotherapy, 3) hormonal therapy, and 4) radioisotope therapy. Sipuleucel-T (Provenge, Dendreon) was the first immunotherapy approved for castration-resistant prostate cancer (CRPC). The administration of sipuleucel-T involves a process by which T cells obtained from an individual patient through leukapheresis are activated against a recombinant prostatic acid phosphatase protein.

In contrast to hormonal agents or cytotoxic agents, sipuleucel-T improves overall survival without impacting progression-free survival.[1] Since a fixed course (3 infusions separated by 2 weeks) is the approved schedule of administration of sipuleucel-T, the disconnect between progression-free survival and overall survival does not influence continuation of the treatment; rather, it makes it a challenge to determine the optimal time to administer the next treatment. This issue is complicated by the fact that several drugs (eg, abiraterone acetate [Zytiga, Janssen Biotech], taxanes) require the concomitant use of steroids, which may

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abrogate the effects of immune therapy. A recent study by Small and colleagues demonstrated that treatment with concomitant abiraterone acetate/prednisone does not have a significant impact on immune parameters in sipuleucel-T patients[2]; unfortunately, the effect of corticosteroids on survival is unknown. Thus, without biological markers to select patients who are more likely to respond to the aforementioned treatment, decisions are based upon relative toxicity of drugs, as well as theoretical synergy or antagonism. These parameters would favor the administration of immune therapy early in the course of castration-resistant disease. It therefore becomes more important to consider the different possible patient types that would be appropriate for each agent.

A recent analysis of the phase III IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial by Schelhammer and associates examined prostate-specific antigen (PSA) quartiles as potential indicators of when patients should receive immunotherapy.[3] The study suggested that patients with lower volumes of disease as measured by PSA tend to do better with sipuleucel-T. Although this finding is consistent with the concept that immune therapy works best in low volumes of disease, one could argue that patient selection bias could also account for these findings. Nonetheless, these findings suggest an advantage for earlier treatment.

The analysis by Schelhammer and associates is interesting. Although a prospective evaluation of these data would be ideal, it will probably not occur because there are now multiple competing drugs in this space.

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