Cellular Immunotherapy for Prostate Cancer

Policy Number: 8.01.53 Last Review: 11/2019
Origination: 07/2015 Next Review: 11/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for cellular immunotherapy for prostate cancer when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Sipuleucel-T therapy may be considered **medically necessary** in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer.

When Policy Topic is not covered
Sipuleucel-T therapy is considered **investigational** in all other situations, including but not limited to treatment of hormone-responsive prostate cancer, treatment of moderate to severe symptomatic metastatic prostate cancer, and treatment of visceral (liver, lung, or brain) metastases.

Considerations
Sipuleucel-T therapy requires prior authorization through the Clinical Pharmacy Department.

All costs of the leukapheresis procedure – including the cell collection and transportation – are covered by Dendreon Corporation, the manufacturer of sipuleucel-T and would be reported using the specific HCPCS code Q2043.

Description of Procedure or Service
Sipuleucel-T (Provenge®; Dendreon Corp.) is a new class of therapeutic agent used in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and are then reinfused back into the patient. The proposed mechanism of action is that treatment stimulates the patient’s own immune system to resist cancer spread.

For patients with metastatic, androgen-independent prostate cancer, 3 randomized controlled trials (RCTs) of sipuleucel-T reported an improvement in median survival of approximately 4 months. The 2 early studies of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third study, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All 3 studies also were consistent in demonstrating that sipuleucel-T does not delay time to measureable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of the treating physician; thus, the survival benefit accrues in the context of additional treatment as needed for symptomatic recurrence. This evidence is sufficient to conclude that sipuleucel-T improves net health outcome for patients with androgen-independent, asymptomatic or minimally symptomatic, metastatic prostate cancer.

For patients who do not meet the previously described criteria, evidence does not demonstrate an
improvement in net health outcome. One RCT of patients with androgen-dependent, nonmetastatic prostate cancer showed no statistical difference between sipuleucel-T and control in time to biochemical failure or prostate-specific antigen (PSA) doubling time. This evidence does not support the use of sipuleucel-T for patients with hormone-responsive prostate cancer, moderate-to-severe symptomatic metastatic prostate cancer, or visceral (liver, lung, brain) metastases.

**Rationale**

**BACKGROUND**

Prostate cancer is the second leading cause of cancer-related deaths among American men, with an estimated incidence of 220,800 cases and an estimated number of 27,540 deaths in 2015.¹ In most cases, prostate cancer is diagnosed at a localized stage and is treated with prostatectomy or radiotherapy. However, some patients are diagnosed with metastatic disease or recurrent disease after treatment of localized disease. Androgen ablation is the standard treatment for metastatic or recurrent disease. Most patients who survive long enough eventually develop androgen-independent prostate cancer. At this stage of metastatic disease, docetaxel, a chemotherapeutic agent, has been demonstrated to confer a survival benefit of 1.9 to 2.4 months in randomized clinical trials.² ³ Chemotherapy with docetaxel causes adverse effects in large proportions of patients, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms. Trials evaluating docetaxel included both asymptomatic and symptomatic patients, and results suggest a survival benefit for both groups. Because of the burden of treatment and its adverse effects, most patients therefore defer docetaxel treatment until cancer recurrence is symptomatic.

Cancer immunotherapy has been investigated as a treatment which could potentially be instituted at the point of detection of androgen-independent metastatic disease before significant symptomatic manifestations have occurred. The quantity of cancer cells in the patient during this time is thought to be relatively low, and it is thought that an effective immune response against the cancer during this interval could effectively delay or prevent progression. Such a delay could allow a course of effective chemotherapy, such as docetaxel, to be deferred or delayed until necessary, thus providing an overall survival benefit.

Sipuleucel-T (Provenge®; Dendreon Corp.) is a new class of therapeutic agent used in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and are then reinfused back into the patient. At reinfusion, the cells are administered as 3 intravenous infusions given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient’s own immune system to resist cancer spread.

**REGULATORY STATUS**

On April 29, 2010, FDA approved Provenge® (sipuleucel-T; Dendreon Corp., Seattle, WA) via a Biologics Licensing Application for "the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer (for autologous use only)."⁴ Approval was contingent on agreement of the manufacturer to conduct a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 men with prostate cancer who receive sipuleucel-T.

**Metastatic, Androgen-Independent Prostate Cancer**

Sipuleucel-T has been studied most definitively in a series of double-blind, placebo-controlled randomized controlled trials (RCTs). These studies were published by Small et al (2006),⁵ Higano et al (2009),⁶ and Kantoff et al (2010),⁷ and were extensively presented in a briefing document available from the U.S. Food and Drug Administration (FDA). Patients enrolled in these trials all had androgen-independent metastatic prostate cancer, were asymptomatic or mildly symptomatic, in good physical health characterized by Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1, and had tumors with positive staining for prostatic acid phosphatase (PAP).
Patients with asymptomatic metastatic prostate cancer were randomized to receive either sipuleucel-T or a control infusion of untreated dendritic cells. Principal outcome was time to disease progression, defined as the time from randomization to the first observation of disease progression. Disease progression could be defined as radiologic progression (based on several imaging criteria), clinical progression (based on prostate cancer–related clinical events, such as pathologic fracture), or pain progression (based on onset of pain corresponding to anatomic location of disease).

Studies were not designed to establish efficacy based on overall survival (OS). On progression of cancer, patients were allowed to have additional treatment as needed including chemotherapy. Patients originally assigned to placebo were allowed to cross over by receiving their own dendritic cells pulsed with PA2024 antigen (recombinant fusion protein comprising human PAP linked to granulocyte-macrophage colonystimulating factor), but prepared from frozen dendritic cells harvested from their initial leukapheresis procedures.

A survival analysis of study 9901A was presented in the FDA briefing document, with caveats that the study was not powered to show a survival effect and that a primary method of survival analysis was not prespecified in the protocol. Using a log-rank test, median survival times were 25.9 months for vaccinetreated patients and 21.4 months for placebo-treated patients, a statistically significant difference (p=0.011). At 36 months, survival rate was 34% for vaccine-treated patients and 11% for placebo-treated patients.

The FDA briefing document shows analyses of possible confounders regarding the survival analysis. After disease progression, patients in both groups received chemotherapy, but the rate of chemotherapy was slightly higher in the placebo group (48% vs 36%, respectively). Examination of the causes of death did not reveal any obvious spurious elevation of noncancer deaths in the placebo group. The published version of study 9901A by Small et al (2006) analyzed the survival data after adjusting for prognostic factors and found a significant association of sipuleucel-T treatment and survival (HR=2.12; 95% confidence interval [CI], 1.31 to 3.44).

Higano et al (2009) pooled survival data from the 2 studies. Pooled analysis showed a 33% reduction in the risk of death (HR=1.50; 95% CI, 1.10 to 2.05; p=0.011). The association was robust to adjustments in imbalances in baseline prognostic factors and postprogression chemotherapy use.

Because these earlier studies did not meet criteria for success for their principal end points, FDA did not approve sipuleucel-T in 2007. A larger phase 3 trial of similar design called IMPACT enrolling 512 patients was designed with a principal end point of OS. Analyses used to support FDA approval reported a 22% reduction in overall mortality in patients treated with sipuleucel-T. Treatment extended median survival by 4.1 months compared with placebo (25.8 months vs 21.7 months, respectively) and improved 3-year survival by a relative 38% compared with placebo (31.7% vs 23.0%, respectively). Results adjusted for subsequent docetaxel use and timing, as well as analyses examining prostate cancer–specific survival, showed similar magnitude and statistical significance of the survival benefit.

Of note, 14% of enrolled subjects in this trial had received prior docetaxel. In retrospective, prespecified, multivariate subgroup analysis, several baseline factors were associated with OS: prostate-specific antigen (PSA), lactate dehydrogenase, hemoglobin, ECOG Performance Status, alkaline phosphatase, and Gleason score. Analysis of PSA by quartiles showed that men in the lowest quartile had the greatest survival benefit with sipuleucel-T: 49% reduced mortality compared with 26% reduced mortality in the second quartile, 19% in the third quartile, and 16% in the highest quartile.

Small et al (2014) pooled data for time to disease-related pain and time to first use of opioid analgesics from all 3 RCTs. Median time to disease-related pain was 5.6 months for sipuleucel-T versus 5.3 months for control (HR=0.82; 95% CI, 0.62 to 1.09). Median time to first use of opioid analgesics was 12.6 months for sipuleucel-T versus 9.7 months for control (HR=0.76; 95% CI, 0.58 to 0.99).

Regarding the safety of sipuleucel-T, most adverse effects were grade 1 and 2 and resolved within 48
hours. The rate of serious adverse events was not statistically different between vaccine- and placebo-treated patients. However, one difficulty in assessing potential adverse effects by comparing sipuleucel-T with placebo is that placebo comprised infusion of untreated dendritic cells, which may cause adverse effects. FDA reviewers expressed concern regarding a possible association of sipuleucel-T with cerebrovascular events; 8 (5%) of 147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared with zero placebo-treated patients in the 2 early trials. In the latest available report of adverse effects reported in the full prescribing information, incidence of stroke was 3.5% in the sipuleucel-T group and 2.6% in the control group, but these figures appear to include data from trials evaluating a different indication. In the FDA review summarizing cerebrovascular event rates from studies 9901A, 9902A, and interim data from IMPACT, incidence of stroke was 4.9% (17/345) in sipuleucel-T treated patients and 1.7% (3/172) in placebo-treated patients (p=0.092). FDA review called the cerebrovascular event rate a "potential safety signal" and included as part of the approval a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 patients with prostate cancer who receive sipuleucel-T.

Section Summary
For patients with metastatic, androgen-independent prostate cancer, 3 RCTs of sipuleucel-T have been published. The 3 RCTs are consistent in reporting an improvement in OS of approximately 4 months compared with placebo. Two trials also reported that 36-month survival was significantly improved for patients receiving sipuleucel-T, with absolute improvements in survival of 9% and 23%. Time to progression was slightly longer in the sipuleucel-T groups, but this difference was not statistically significant. Serious adverse events were not increased in the sipuleucel-T group. There has been concern raised about a possible increase in stroke risk, but the available trials do not show a significantly increased incidence of stroke.

Other Indications
A phase 3 trial of sipuleucel-T in the setting of androgen-dependent, nonmetastatic prostate cancer was published in 2011. Patients with prostate cancer detectable by PSA after radical prostatectomy received 3 to 4 months of androgen suppression therapy and were then randomized (2:1) to receive sipuleucel-T (n=117) or control (n=59). The primary end point was time to biochemical failure. There was no difference in this end point between groups; median time to biochemical failure was 18.0 months for sipuleucel-T and 15.4 months for control (HR=0.936, p=0.737). Sipuleucel-T patients had a 48% increase in PSA doubling time after testosterone recovery (155 days vs 105 days; p=0.038). Sixteen percent of patients developed distant failure. The treatment effect favored sipuleucel-T but was not statistically significant (HR=0.728, p=0.421).

Section Summary
A single RCT has been performed in patients with androgen-dependent, nonmetastatic prostate cancer, and this trial did not show any benefit for sipuleucel-T compared with control. Therefore, evidence on treatment of nonmetastatic prostate cancer is not sufficient to determine that health outcomes are improved.

Summary of Evidence
For patients with metastatic, androgen-independent prostate cancer, 3 randomized controlled trials (RCTs) of sipuleucel-T reported an improvement in median survival of approximately 4 months. The 2 early studies of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third study, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All 3 studies also were consistent in demonstrating that sipuleucel-T does not delay time to measureable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of the treating physician; thus, the survival benefit accrues in the context of additional treatment as needed for symptomatic recurrence. This evidence is sufficient to conclude that sipuleucel-T improves net health outcome for patients with androgen-independent, asymptomatic or minimally symptomatic, metastatic prostate cancer.
For patients who do not meet these criteria, evidence does not demonstrate an improvement in net health outcome. One RCT of patients with androgen-dependent, nonmetastatic prostate cancer showed no statistical difference between sipuleucel-T and control in time to biochemical failure or prostate-specific antigen doubling time. This evidence does not support the use of sipuleucel-T for patients with hormone-responsive prostate cancer, moderate-to-severe symptomatic metastatic prostate cancer, or visceral (liver, lung, brain) metastases.

REFERENCES

Billing Coding/Physician Documentation Information

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<th>Code</th>
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<td>Q2043</td>
<td>Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion</td>
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Code Q2043 is specific to Provenge and is effective for dates of service on or after July 1,
2011. All costs of the leukapheresis procedure – including the cell collection and transportation – are covered by Dendreon Corporation, the manufacturer of sipuleucel-T. Claims billing separately the apheresis or infusion (36511 or 96365) will be considered incidental to Q2043.

Malignant neoplasm of prostate

**Additional Policy Key Words**

**Policy Implementation/Update Information**

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<td>09/01/11</td>
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