BlueCross BlueShield of Kansas City

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Cellular Immunotherapy for Prostate Cancer

Policy Number: 8.01.53
Origination: 11/2010
Last Review: 11/2014
Next Review: 11/2015

Policy

BCBSKC 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 (hormone-refractory) 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 (hormone-refractory), metastatic prostate cancer. The agent consists of specially treated dendritic cells obtained from the patient with 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 the treatment stimulates the patient's own immune system to resist spread of the cancer.

Background

Prostate cancer is the second leading cause of cancer-related deaths among American men with an estimated incidence of 218,890 cases and an estimated number of 27,050 deaths in 2007. In most cases, prostate cancer is diagnosed at a localized stage and is treated with prostatectomy or radiation therapy. 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. However, 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. (1,2) Chemotherapy with docetaxel causes adverse effects in large proportions of patients, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms. The trials evaluating docetaxel included both asymptomatic and symptomatic patients, and results suggested a survival benefit for both

groups. Because of the burden of treatment and its adverse effects, most patients therefore defer docetaxel treatment until the 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 interval is thought to be relatively low, and it is thought that an effective immune response against the cancer during this time period 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 (hormone-refractory), metastatic prostate cancer. The agent consists of specially treated dendritic cells obtained from the patient with 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 IV infusions, each infusion given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient’s own immune system to resist spread of the cancer.

Regulatory Status
On April 29, 2010, the U.S. Food and Drug Administration (FDA) approved Provenge® (sipuleucel-T, Dendreon Corp.) via a Biologics Licensing Application (BLA) for "the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer (for autologous use only)." 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 1,500 patients with prostate cancer who receive sipuleucel-T.

Rationale

Sipuleucel-T has been studied most definitively in a series of double-blind, placebo-controlled studies. (3) Results of 2 of these studies have been published by Small et al. (4) and Higano et al. (5) and extensively presented in a briefing document available from the U.S. Food and Drug Administration (FDA). (6) Results of the third and largest trial are not published but were presented at the American Urological Association meeting in April 2009 and summarized in an FDA press release in April 2010. (7) 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.

In the 2 early identically designed studies, (3–6) patients with asymptomatic metastatic prostate cancer were randomized to receive either sipuleucel-T or a control infusion of untreated dendritic cells. The principal outcome of these studies 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).

The studies were not designed to establish efficacy based on overall survival. Upon 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, but prepared from frozen dendritic cells harvested from their initial leukapheresis procedures.

Table 1. Description of randomized Phase III trials of sipuleucel-T

Study name	Design	Eligibility	Treatment	Outcomes
9901A 9902A	Randomized, double blind, placebo-controlled	Metastatic prostate cancer by imaging, asymptomatic and progressing by imaging or rising PSA	Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells	Primary: Disease progression (radiological, clinical, pain) Secondary: Time to pain, time to progression
IMPACT	Randomized, double blind, placebo-controlled	Metastatic prostate cancer by imaging, asymptomatic or minimally symptomatic and progressing by imaging or rising PSA	Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells	Primary: Overall survival Secondary: Time to objective disease progression

Ctl: control arm; Exp: experimental arm; PSA: prostate-specific antigen

Results of study 9901A for the principal outcome of time to progression did not show a significant difference between vaccine and control. Median time to progression was 11.7 weeks for the vaccine group and 10.0 weeks for the control group.

A survival analysis of study 9901A was presented in the FDA briefing document, with the 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. The median survival times for vaccine-treated patients was 25.9 months and for placebo-treated patients was 21.4 months, which was statistically significant (p=0.011; log-rank test). At 36 months, the survival rate was 34% for vaccine-treated patients and 11% for placebo-treated patients.

The FDA briefing document (6) 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-treated groups (48% versus 36%, respectively). Examination of the causes of death did not reveal any obvious spurious elevation of non-cancer causes of death in the placebo group. The published version of study 9901A by Small et al. (4) analyzed the survival data after adjusting for prognostic factors and found a significant association of sipuleucel-T treatment and survival (hazard ratio [HR]: 2.12; 95% confidence interval [CI]: 1.31–3.44).

Because study 9901A did not meet its principal outcome endpoint for efficacy, enrollment for its partner study 9902A was suspended. Its sample size was therefore smaller, and the study subsequently had lower statistical power. Results for study 9902A showed a median time to progression of 10.9 weeks in the vaccine group versus 9.9 weeks in the placebo group, which was not statistically significant. A survival analysis of study 9902A showed that vaccine-treated patients had a median survival of 19 months, and control patients had a median survival of 15.7 months, which was also not statistically significant.

The two studies' survival data were pooled in the study by Higano et al. (5) The pooled analysis showed a 33% reduction in the risk of death (HR: 1.50; 95% CI: 1.10–2.05, p=0.011). The association was robust to adjustments in imbalances in baseline prognostic factors and post-progression chemotherapy use.

Because these earlier studies did not meet criteria for success for their principal endpoints, the FDA did not approve sipuleucel-T in 2007. A larger Phase III trial of similar design called IMPACT enrolling 512 patients was designed with a principal endpoint of overall survival. Analyses reported at the American Urological Association in April 2009 and 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 to placebo (25.8 months versus 21.7 months, respectively) and improved 3-year survival by a relative 38%, compared to placebo (31.7% versus 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 treatment.

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 to placebo is that the placebo consisted of infusion of untreated dendritic cells, which may cause adverse effects. Concern was expressed in the FDA review regarding a possible association with cerebrovascular events, as 8/147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared to zero placebo-treated patients in the 2 early trials. (6) In the latest available report of adverse effects reported in the full prescribing information documents, (3) the stroke rate 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, the rate was 4.9% (17/345) in the sipuleucel-T-treated subjects and 1.7% (3/172) in placebo-treated subjects (p=0.092). The 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 1,500 patients with prostate cancer who receive sipuleucel-T.

Summary

The results of 3 randomized, controlled trials of sipuleucel-T given in the setting of asymptomatic or mildly symptomatic androgen-independent metastatic prostate cancer show an improvement in median survival of 4 months. The 2 early studies of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but showed survival effects consistent with the third study, which was designed to demonstrate a mortality difference. All 3 studies are also consistent in demonstrating that sipuleucel-T treatment does not delay time to measureable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of their 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 is medically necessary for patients with androgen-independent, asymptomatic or minimally symptomatic, metastatic prostate cancer.

Table 2. Results of randomized, Phase III trials of sipuleucel-T

Study 9901A			
	Vaccine n=82	**Control n=45**	**p value**
Median time to progression	11.7 weeks	10.0 weeks	0.052
Median time to clinical progression	10.7 weeks	9.1 weeks	0.061
Overall median survival	25.9 months	21.4 months	0.01
Overall survival at 36 months	34%	11%	0.005 Multivariable adjusted 0.002
Study 9902A			
	Vaccine n=65	**Control n=33**	**p value**
Median time to progression	10.9 weeks	9.9 weeks	0.719

Overall median survival	19.0 months	15.7 months	0.331
IMPACT study			
	Vaccine n=341	**Control n=171**	**p value**
Overall median survival	25.8 months	21.7 months	0.032
Overall survival at 36 months	31.7%	23.0%	0.036
Time to progression	Not reported	Not reported	Hazard ratio: 0.95 p=0.628

Other Indications
A Phase III trial of sipuleucel-T in the setting of androgen-dependent, nonmetastatic prostate cancer was published in 2011. (8) Patients with prostate cancer detectable by PSA following 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 endpoint was time to biochemical failure. There was no difference in this endpoint 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 following testosterone recovery (155 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).

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer were updated on May 25, 2010 to add sipuleucel-T as a category 1 treatment recommendation for patients with castration-recurrent prostate cancer. (9) A note was also added indicating that sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1; and it is not recommended for patients with visceral disease and a life expectancy less than 6 months.

Medicare National Coverage
On June 30, 2011 a national coverage determination was released by CMS approving sipuleucel-T for treatment of asymptomatic or minimally symptomatic castrate-resistant prostate cancer. Coverage for off-label indications was left to the discretion of local Medicare administrative contractors.

References:

1. Berry DL, Moinpour CM, Jiang CS et al. Quality of life and pain in advanced stage prostate cancer: results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone. J Clin Oncol 2006; 24(18):2828-35.
2. Tannock IF, de WR, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351(15):1502-12.
3. Dendreon Corporation. Seattle W. Provenge® (sipuleucel-T) prescribing information. 2010. Available online at: http://www.provenge.com/pdf/prescribing-information.pdf. Last accessed June 2013.
4. Small EJ, Schellhammer PF, Higano CS et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006; 24(19):3089-94.
5. Higano CS, Schellhammer PF, Small EJ et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer 2009; 115(16):3670-9.
6. U.S. Food and Drug Administration. Cellular Tissue and Gene Therapies Advisory Committee Meeting. Clinical Briefing Document: Provenge (Sipuleucel T). March 29, 2007. Available online at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_2a.pdf. Last accessed June 2013.

7. U.S. Food and Drug Administration. Press release: FDA Approves a Cellular Immunotherapy for Men with Advanced Prostate Cancer. 2010. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210174.htm. Last accessed June 2013.
8. Beer TM, Bernstein GT, Corman JM et al. Randomized trial of autologous cellular immunotherapy with sipuleucel-T in androgen-dependent prostate cancer. Clin Cancer Res 2011; 17(13):4558-567.
9. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology V. Prostate Cancer. 2010. Available online at: http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf. Last accessed May 2010.
10. Mohler JL, Armstrong AJ, Bahnson RR et al. Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2012; 10(9):1081-7.
11. Center for Medicare and Medicaid Services. National Coverage Determination (NCD) for Autologous Cellular Immunotherapy Treatment (110.22), 6/30/2011. 2011. Available online at: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=344&ncdver=1&bc=AAAAgAAAAAAA&. Last accessed June 2013.

Billing Coding/Physician Documentation Information

Q2043 Sipuleucel-t, minimum of 50 million autologous cd54+ cells activated with pap-gm-csf, including leukapheresis and all other preparatory procedures, per infusion

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.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

11/1/10	New policy; may be considered medically necessary.
9/1/11	Coding updated.
11/1/11	No policy statement changes.
11/2014	No policy statement changes