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Courtney Porter  
Ohio Northern University

Joshua Ilenin  
Ohio Northern University

Lisa Berni  
Ohio Northern University

Ashley Overy  
Ohio Northern University

Karen L. Kier  
Ohio Northern University, k-kier@onu.edu

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Sipuleucel-T (Provenge®): Therapeutic Use and Financial Implications

Courtney Porter, a fourth-year pharmacy student from Canfield, Ohio; Joshua Ileenin, a fourth-year pharmacy student from Mantua, Ohio; Lisa Berni, a fifth-year pharmacy student from Dennison, Ohio; Ashley Overy, a fifth-year pharmacy student from Grafton, Ohio; Karen Kier, BSpH '82, Ph.D., R.Ph., BCPS, professor of clinical pharmacy and director of the non-traditional doctor of pharmacy program

Abstract
Although mortality rates have been declining, prostate cancer accounts for a large percentage of cancer diagnoses worldwide. Sipuleucel-T (Provenge®), an autologous cellular immunotherapy targeted against the antigen expressed in most prostate cancers, has been shown to increase the median survival rate of castration-resistant prostate cancer. Even so, the therapeutic risks and benefits, as well as financial implications, all currently play a role in the governmental decision to reimburse for this new therapy.

According to the National Comprehensive Cancer Network (NCCN), prostate cancer accounted for 25 percent of cancer diagnoses in men during 2009.1 While this incidence is high, the mortality rates from prostate cancer have been declining due to earlier detection and treatment through increased public awareness. However, earlier treatment of non-life-threatening prostate cancer also may lead to the occurrence of seemingly unnecessary side effects and even impaired quality of life. The risks and benefits associated with treating prostate cancer at this minimally symptomatic stage, especially its financial implications, all play a role in the decision of insurance companies to reimburse the therapeutic use of a new drug. This is the case for sipuleucel-T (Provenge®), a novel treatment for castration-resistant prostate cancer that is currently being evaluated by Medicare for reimbursement eligibility.

Several factors are taken into consideration when treating a patient with prostate cancer, including their estimated life expectancy, comorbidities, therapy side effects, and patient preference.1 The selected treatment is also based on the patient’s assigned risk group. The assigned risk group is a designated placement that considers the patient’s Gleason grade, prostate specific antigen (PSA) level, and pathologic staging of the cancer, all of which determine the cancer’s overall severity. Historically, treatment has included active surveillance of the tumor, radiation, surgery, androgen deprivation therapy, and/or chemotherapy.

Sipuleucel-T is an autologous cellular immunotherapy targeted against the antigen expressed in most prostate cancers, prostate acid phosphatase (PAP).2 The therapeutic vaccine contains mononuclear cells, including antigen-presenting cells (APCs), which are obtained from the patient’s blood. These cells are cultured with PA2024, a fusion protein made up of PAP fused to granulocyte-macrophage colony-stimulating factor (GM-CSF).3 Although the mechanism of action is not entirely clear, it is thought that once administered to the patient, the APCs present the antigen to T lymphocytes which elicit an immune response against the antigen.

About three days before infusion, the patient has blood drawn, and the autologous APCs are obtained via leukapheresis.2 These cells are sent to the manufacturing facility, cultured with the fusion protein, and then sent back to the clinic where the prepared infusion can be administered to the patient. Sipuleucel-T is given at two-week intervals for three doses.3 Approximately 30 minutes before each infusion, the patient must be pre-medicated with acetaminophen and an antihistamine as prophylactic treatment for infusion-related events. Common adverse reactions associated with sipuleucel-T include acute infusion reactions, chills, fatigue, fever, back pain, nausea, joint ache, and headache.4

The immunotherapy provided by sipuleucel-T introduces a novel type of drug therapy that can increase the median survival rate of castration-resistant prostate cancer by an average of four months (from 21.7 months to 25.8 months).5 This is according to the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial, the double-blind, placebo-controlled, multicenter phase 3 study that persuaded the Food and Drug Administration (FDA) to approve the drug. This study also found that sipuleucel-T reduced the risk of death by 22 percent relative to the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P=0.03) and increased the 36-month survival probability from 23.0 percent in the placebo group to 31.7 percent in the sipuleucel-T group. However, questions have been raised in regards to the IMPACT trial through an editorial published by The New England Journal of Medicine.6 This editorial specifically addresses the GM-CSF received through sipuleucel-T’s administration and its potential benefit in fighting the cancer.7 It proposes that the increase in median survival rate established by this trial may not only be associated with the drug, but with the overall stimulation of the immune system provided by GM-CSF. If this is the case, the editorial states that the placebo group should also have received GM-CSF to produce more of an effect on the median survival rate of patients treated with sipuleucel-T.

In comparison to the other available treatments, NCCN guidelines for prostate cancer only recommend sipuleucel-T for asymptomatic or minimally symptomatic patients with a life expectancy greater than six months and with no visceral disease. This is due to the inability to directly measure the drug’s effect since the normal markers of improvement for prostate cancer, including a decline in PSA or improvement of bone or CT scans of metastasized tumors, are not observed. Currently, docetaxel with prednisone or mitoxantrone with prednisone are the first-line treatments recommended for this type of prostate cancer and have been shown to demonstrate a survival rate of 18.9 months and 16.5 months, respectively.4

The economic implications of many cancer treatment options have come under increased scrutiny in recent years. Since chemotherapeutic agents often represent some of the most expensive FDA-approved medications currently available, critics argue that their overall benefit to patients should be closely studied before these medications gain final approval.8 Medications used to treat cancers that have reached the metastatic stage, such as sipuleucel-T, are even more controversial due to their mostly marginal increases in patient quality of life or life expectancy with a given disease. In order to accurately measure the value of
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a pharmacologic therapy, cost-utility analyses (CUAs) are commonly used.8,9 CUAs are a special type of cost-effectiveness study that use quality-adjusted life years (QALYs) to evaluate the overall benefits of a drug. According to the National Institute for Health and Clinical Excellence (NICE), using QALYs provides a means of estimating the number of quality months or years that an individual can expect to live if they undergo a given treatment.10 In these studies, life quality is calculated using an aggregation of different variables, including a patient’s pain level, overall mobility and disposition. This type of analysis is well-suited for studying chemotherapy agents, such as sipuleucel-T, because QALYs represent a measure of success for many types of metastatic or incurable cancers. The current NICE threshold for cost-effective therapy is £20,000-£30,000 ($32,548-$48,882) per QALY and is considered a benchmark for new medications to meet in order for final FDA approval.

Currently, the required three doses of sipuleucel-T cost approximately $93,000.11,12 Given the 4.1-month median increase in life expectancy for patients in its pivotal clinical trial, sipuleucel-T’s cost per month of extended life is around $23,000.12 These cost estimates, however, only included the amount the pharmaceutical company charges to formulate each individual patient’s doses. Additional costs, such as those associated with the leukapheresis procedures required to harvest an individual’s cells and administrative expenses, probably make the total cost to patients much higher than the initial estimate. In addition to these costs, critics argue, many patients using sipuleucel-T still require traditional chemotherapy, increasing the overall treatment costs even more. While there are currently no guidelines in place governing the QALY cost threshold in the United States, a widely accepted limit of $50,000 per QALY is one means to evaluate sipuleucel-T.13 In spite of the expense, many large private insurance companies, including Humana, Aetna, Kaiser Permanente, Cigna, and AmeriHealth, have already chosen to cover the cost of three treatments in patients with asymptomatic or minimally symptomatic, metastatic castrate-resistant prostate cancer.4,14,15 While coverage by private insurers has largely been uncontested, the Centers for Medicare and Medicaid Services (CMS) announced in June 2010 that they would perform a national coverage analysis (NCA) at the request of local Medicare contractors. The purpose of an NCA is to allow for public comments on sipuleucel-T and the benefits and risks that have been experienced in real-world patients treated with the drug. The NCA is expected to last until mid-2011, and the results of this CMS review will ultimately dictate Medicare’s final position on sipuleucel-T coverage.16

As of March 30, 2011, Medicare’s NCA of sipuleucel-T had completed, and the overall therapeutic and economic balance of its risks and benefits tipped the scales in its favor.16 Sipuleucel-T’s statistically significant 4.1-month increase in median survival rate, mild adverse effects, and acceptable but controversial CUA supported the FDA’s intention of use in patients and persuaded Medicare to reimburse payment for its indicated use as private insurers have already done. The drug’s specific target treatment population of castration-resistant prostate cancer had a positive effect in Medicare’s decision, especially since it is the only remaining systemic treatment currently approved for use in these patients other than chemotherapy. Pending a 30-day period allowing an opportunity for public comment, Medicare will issue a memorandum stating this final decision. While Medicare has not approved of-label use of this immunotherapy due to inadequate evidence demonstrating sipuleucel-T’s effectiveness in other treatment populations, it has decided to allow local contractors to determine eligibility for other proposed uses, but it would be willing to reconsider this decision if more evidence presents itself in the future. Although at a high cost to taxpayers, Medicare’s decision to cover the use of sipuleucel-T offers the possibility of an extended life expectancy to affected Americans.

References


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