

Approval of Provenge Seen As First Step for Cancer Treatment Vaccines

By Vicki Brower

A decade in development, Dendreon's prostate cancer vaccine, sipuleucel-T (Provenge), has become the first therapeutic cancer vaccine to receive approval from the U.S. Food and Drug Administration. The FDA approved Provenge in April to treat metastatic castration (hormone)-resistant prostate cancer.

In the phase III trial, known as IMPACT, patients taking Provenge had a 4.1-month median improvement in overall survival. Although 4 months is a modest increase, some view Provenge's approval as a milestone for the entire class of immunotherapeutic cancer vaccines.

"Provenge's approval is a watershed," said Charles G. Drake, M.D., Ph.D., who works on prostate cancer and vaccine development at Johns Hopkins' Kimmel Cancer Center in Baltimore. "It represents a formal proof of principle that the immune system can be used to treat cancer."

But others, such as William Dale, M.D., Ph.D., a geriatrics specialist and prostate cancer researcher at the University of Chicago Medical Center, are less sure. Dale notes that although the vaccine improved overall survival in the IMPACT trial, it did not improve time to progression. "There is no evidence that increased survival here is cancer related. The hype is a little too much for the benefits observed," said Dale, who is not involved in vaccine development. "I'd like to see more evidence of a disease-specific response."

IMPACT's primary investigator, Philip Kantoff, M.D., of Boston's Dana-Farber Cancer Institute, acknowledges that "we don't know exactly how it works or how best to give it." Like others, he sees Provenge as a first step for cancer immunotherapy.

How Provenge works is one of many unanswered questions about treatment vaccines. For instance, the best way to measure

progression after treatment with immunotherapies is not clear, according to Kantoff, who speculates that measurement issues may help explain the lack of improvement in progression-free survival time in the IMPACT trial. Questions also remain about the direct and indirect effects of immune therapies on cancer cells and their microenvironments, at what stage of disease vaccines should be used, and how they can best be combined with other treatments.

But even as they address these issues, Dendreon and other companies are moving ahead with development of more vaccines for prostate and other cancers.

Road to Approval

Provenge, designed to stimulate T cells to attack cancer cells, is an autologous vaccine—it is personalized for each patient, using his or her own cells. Antigen-presenting cells are removed by leukapheresis on day 1; processed with a tumor antigen called prostatic acid phosphatase, which is found on prostate cancer and normal prostate cells, on days 2 and 3; and then fused to granulocyte-macrophage colony-stimulating factor (GM-CSF). Patients receive an infusion on day 3 or 4, and twice more, in weeks 2 and 4.

Compared with some forms of chemotherapy, Provenge's side effects are mild. Safety data from four phase III Provenge trials with nearly 600 men showed that 83.4% of those treated were fully active and could perform predisease activities without restrictions during treatment, according to Simon Hall, M.D., chairman of urology at Mount Sinai School of Medicine in New York. Hall presented the IMPACT results in May at the American Urological Association meeting in San Diego. Half the participants had fever, chills, and backaches, which were gone within 2 days, and only 3% had grade 3 or higher adverse effects. One concern,

however, was a slightly higher incidence of cerebral hemorrhage among those taking the vaccine. Dendreon is monitoring patients for this side effect over the next year.

Provenge has had a rocky road to market. On the basis of the first two phase III trials, with 127 and 99 patients, Dendreon filed for approval several years ago. But in March 2007, the FDA deferred approval, noting that the two trials had missed the primary endpoint, progression-free survival.

At the time, Howard Scher, M.D., chief of the genitourinary service at Memorial Sloan-Kettering Cancer Center in New York, who served on the FDA advisory board, urged in a letter to the FDA that it wait until Dendreon completed a 512-patient trial, whose primary endpoint was overall survival.

The absence of other signs of an antitumor effect reinforced Scher's concerns about the validity of the findings. "Specifically, there was no evidence of a favorable effect on prostate-specific antigen, tumor regression, or stabilization of soft tissue or bony disease radiographically, or health-related quality of life," he said.

In August 2009, Dendreon published results from its third large trial and filed for approval on the basis of all three trials.

Provenge ultimately succeeded where others had not for many reasons, experts say.

It used a large, quantified number of antigen-presenting cells, administering them intravenously, not by subcutaneous or intradermal injection. It transformed cells under controlled conditions *ex vivo* rather than in the body's immunosuppressed milieu. And it combined a well-defined tumor antigen with an immunostimulating molecule.

"Previous vaccines were less purified, cruder mixtures of patients' tumors, without well-defined tumor antigens at sufficient strengths," said Larry Kwak, M.D., Ph.D.,

professor and chair of the department of lymphoma and melanoma at the M. D. Anderson Cancer Center in Houston, who is developing a lymphoma vaccine.

"While not a cure, Provenge is a foot in the door and shows us a way forward," he said. "It's an exciting time for cancer vaccines."

Dendreon plans to produce peptide fusion vaccines for bladder, breast, and gastric cancers by using different antigens fused to GM-CSF. It will file an investigational new-drug application with the FDA late this year for bladder cancer and then will file applications yearly for other cancers. During the first 12 months after approval, while the company ramps up manufacturing, 2,000 patients will receive the prostate vaccine, according to Mark Frohlich, M.D., Dendreon's senior vice president for clinical affairs and chief medical officer. Fifty medical centers that conducted phase III trials have access to the vaccine during this first year. Physicians at those centers determine which patients to treat.

The Competition

Meanwhile, other therapeutic prostate cancer vaccines are in development. Bavarian Nordic Immunotherapeutics is developing Prostavac-VF, an allogeneic vaccine based on two poxviruses and prostate-specific antigen along with three costimulatory molecules, which is given monthly, subcutaneously, in seven doses. It produced an improved overall survival of 8.5 months (25.1 versus 16.6 months) com-

pared to placebo in a randomized phase II trial. The company's CEO, Reiner Laus, M.D., and James Gulley, M.D., Ph.D., from the National Cancer Institute presented the findings at the American Society of Clinical Oncology's annual meeting in June. Like Provenge, however, Prostavac-VF did not improve time to progression. It will soon start phase III trials.

"Provenge's approval is a watershed. It represents a formal proof-of-principle that the immune system can be used to treat cancer."

"The hype is a little too much for the benefits observed. I'd like to see more evidence of a disease-specific response."

One of the first therapeutic cancer vaccines, GVAX, originally developed by Cell Genesys, failed in a phase III prostate cancer trial. However, a phase II trial by BioSante Pharmaceuticals will retest it this year. GVAX is an allogeneic vaccine made from tumor cells engineered to produce GM-CSF and then irradiated and injected subcutaneously.



Charles G. Drake, M.D., Ph.D.

In this trial, Johns Hopkins' Drake will test GVAX as a neoadjuvant therapy, combined with low-dose chemotherapy. Unlike the previous trials, this one will enroll patients with earlier-stage disease, "where it has a better chance of working," Drake said. "If that combination works—and we will know when we see immune cells in the removed prostates—then we will go forward with a trial in biochemically relapsed disease," he said.

A third prostate cancer vaccine, Northwest Biotherapeutics' DCVax, is an autologous dendritic cell vaccine that uses prostate-specific membrane antigen as the antigen. It is cleared for phase III testing in 600 men with nonmetastatic hormone-independent disease. The primary endpoint is progression-free survival, with overall survival the secondary endpoint. Phase II trials with this vaccine showed a 38.7-month median overall survival, with 64% overall survival at 3 years. In non-



William Dale, M.D., Ph.D.

metastatic disease, the median time to progression was 59 weeks, and median survival, at 54 weeks, had not been reached as of the last long-term follow-up. Some, like Drake, predict that immunotherapeutic vaccines will be more effective in nonmetastatic disease, before patients become highly immune suppressed and tumor burden increases. "Giving the vaccine before surgery and radiation but before chemotherapy makes sense because of the immunosuppressive effects of chemo," Hall said.

Provenge is also now in an open-label phase II trial as neoadjuvant treatment [before radical prostatectomy] in men with localized prostate cancer. They will receive three infusions before surgery and will, on a randomized basis, receive either a booster or no treatment afterward.

Researchers may also try other strategies to improve outcomes. For instance, finding better adjuvants to stimulate a stronger immune response and combining vaccines with other agents might produce better results, Kwak said.

The Cost

As Provenge moves into the clinic, its cost to patients—\$93,000 for three infusions—could

be an issue. Dendreon's Frohlich maintains that with few side effects, "its price tag may not reflect the true cost to the health care system." He pointed out that docetaxel, a standard treatment for prostate cancer, costs \$18,000, but that does not include the cost of supportive care for its considerable side effects.

Frohlich's optimism may be well founded. On May 12, the National Comprehensive Cancer Network rated Provenge as category 1, recommending it as a salvage therapy for fully active, hormone-refractive patients. With this rating, insurers are unlikely to refuse coverage.

Medicare uses the National Comprehensive Cancer Network compendium of

drugs and usually pays for drugs when used according to their FDA-approved indications. However, in late June, CMS announced it would conduct a National Coverage Analysis on Provenge, introducing an element of uncertainty; if the decision is negative, many prospective users, possibly most, could be denied coverage. The public comment period on Medicare coverage of Provenge ends July 30, and a decision is expected after March 30, 2011.

Dr. Drake has served as a consultant to Dendreon. Dr. Kantoff has received research support from Dendreon.

© Oxford University Press 2010. DOI: 10.1093/jnci/djq295