Early-Stage Progress on Glioma Vaccines

By Vicki Brower

A n experimental vaccine for glioblastoma patients showed promise in a recent Phase II study. The peptide-based immunotherapy vaccine, CDX-110, also known as rindopepimut, is designed to mobilize the immune system to attack only malignant cells which express a mutant protein, EGFRvIII, which fuels the unchecked growth of cancer cells. Only 30% of glioblastoma patients carry this mutation.

Forty-three of the 65 patients (66%) enrolled in the study were progression-free at 8.5 months from diagnosis, or 5.5 months from start of vaccination, compared to a progression-free rate in matched historical controls of 53% (Journal of Clinical Oncology preprint, Oct. 4, 2010). Although the results should only be considered preliminary—since they are from Phase I and II trials, which are not controlled, and not designed to detect survival benefits—they have made some researchers optimistic about the future of vaccines for glioblastoma.

“The trial indicates that the immune system can be induced to recognize a cancer-specific antigen, cross the blood-brain barrier, and mount a significant enough immune response to affect mortality.”

A New Era for Cancer Vaccines?

CDX-110, which is made by CellDex Therapeutics, is one of a handful of immunotherapy vaccines in early-to-mid-stage testing for glioma that may change the dire outlook of this disease. With about 10,000 patients a year diagnosed with the disease and half dying from it within 12 months, glioblastoma has long been considered to be one of the most lethal malignancies. It is typically treated with surgery, radiation, and chemotherapy. The chemotherapy temozolomide, introduced in 2005, was the first treatment in decades to improve prognosis, but only from a median of 12 months to 14.6 months for PFS. Such a modest improvement came the same year as a study indicating that overall treatment of this malignancy is uneven at best, and that new treatments were urgently needed (see JNCI 2005: 97:478-9).

Immunotherapy vaccines, which account for only about one-fifth of all oncology therapeutics in the pipeline, have been plagued by slow progress, primarily due to the challenge of producing a powerful enough immune response in patients whose immune systems are already compromised. “Results with cancer vaccines have been disappointing on the whole until relatively recently,” said Garo Armen, Ph.D., co-founder and CEO of Agenus, formerly Antigenics, of Lexington, Mass.

One of the major challenges to vaccine development has been to understand how activated T cells are neutralized by tumors, Armen said. Researchers have made progress in this area in the past year, notably with the FDA’s approval of Bristol Myers Squibb’s ipilimumab, a monoclonal antibody shown to improve overall survival for patients with advanced melanoma. “In the future, it will be possible to combine cancer vaccines with the anti-CTLA-4 antibody, ipilimumab, which augments T cell responses necessary to mount a tumor-specific immune response,” said Armen.

Other chemotherapy agents, such as sunitinib and temozolomide, which studies have shown to increase the effects of regulatory T cells, can be added to vaccine regimens, according to John Yu, M.D., director of the Brain Tumor Center at Cedars-Sinai Medical Center in Los Angeles, Calif.

Yu added that vaccines produce the best results in newly diagnosed patients in whom most of the tumor has been resected. “Younger patients, who generally have stronger immune systems, as well as those with minimal tumor burden, seem to do best,” said Yu.

Immunotherapeutic vaccines have distinct advantages over chemotherapy, Yu said. “They are highly specific for cancer cells, and as such, produce relatively minor toxicities.” Vaccines can also “recognize” and kill cancer cells regardless of cell cycle, unlike most chemotherapies, which mainly attack rapidly dividing cells. And, resistant tumors are amenable to treatment with vaccines because some of the same tumor antigens being targeted are also associated with resistance. Glioma-associated antigens, including TRP-2, HER-2, EGFR, and Ephα2, are not only T cell targets; they also mediate drug resistance. Yu has demonstrated that targeting TRP-2 with cytotoxic lymphocytes increased sensitivity to chemotherapy (Oncogene 23: 9392-400).

Dendritic Cell Vaccines

ImmuNoCellular Therapeutics of Los Angeles, where Yu serves as chief scientific officer and chairman, targets a population of chemotherapy- and radiation-resistant cancer stem and daughter cells bearing the CD133 marker. One of the reasons gliomas are so resistant to treatment, many believe, is the role tumor stem cells play in oncogenesis, in reseeding tumor regrowth. In a 2006 study, Yu, Keith Black, M.D., and colleagues found that 10.2% to 69.7% of the cells in these three glioblastoma patient cell lines express CD133.

One vaccine-based treatment for glioblastoma is ICT-107, which uses autologous, dendritic, or antigen-presenting cells. It is produced by extracting patients’ dendritic cells from their blood and loading the cells with four antigens, TRP2, GP100, HER2, and K13ra, which are highly expressed on glioma stem cells. “Like Dendreon, we use dendritic cells, which are also very powerful adjuvants, for antigen presentation, to activate CD8 cells and elicit a powerful T cell response,” Yu said. Previous research indicates that this vaccine also acts synergistically with temozolomide.

Results from a Phase I trial in newly diagnosed patients receiving standard treatment showed two-year survival rates of 80%, compared to the historical median of about 36%. One patient out of 16 is disease-free
after nearly four years. No treatment-related serious adverse effects have been seen yet. A Phase II randomized, placebo-controlled trial with 102 patients will soon begin, as will a Phase I trial in pediatric patients.

A second autologous dendritic cell vaccine, DCVax-Brain, being developed by Northwest Biotherapeutics of Bethesda, Maryland, uses tumor lysate from each patient which contains multiple antigens. It is also pulsed with dendritic cells, said lead investigator Linda M. Liau, M.D., Ph.D., professor of neurosurgery at the University of California in Los Angeles.

DCVax-Brain has completed Phase I studies in 28 patients, 23 with grade IV glioblastoma and 5 with grade III anaplastic glioma. In this dose-escalation study, the vaccine was given after surgery, and afterward patients were given standard radio-chemotherapy every other week, for three injections, then in between monthly cycles of temozolomide. For recurrent glioblastoma patients, the three biweekly vaccine injections were given at the earliest feasible date after patients recovered from surgery and finished steroids. Side-effects were limited mostly to rashes near the injection site and flu-like symptoms.

Following the initial vaccination series, patients received booster vaccinations with agonists of toll-like receptors, TLRs, a class of proteins which play a key role in the innate immune system, every three months until tumor progression. “The role of the TLR agonists was to act as immune adjuvants to enhance the efficacy and durability of the vaccine,” Liau said. Also preliminary, results with this Phase I study showed that the vaccine was associated with a median survival of over 31 months, about double the rate of historical controls. These results were published in the March 15th issue of Clinical Cancer Research. (Clin Cancer Res. 2011 Mar 15;17(6):1603–15. Epub 2010 Dec 6). Liau cautioned that these findings must be confirmed in larger, randomized studies.

Using gene expression profiling, Liau also found that patients with the mesenchymal subtype of the disease, which typically has the worst prognosis, had the highest number of CD3 and CD8 tumor-infiltrating lymphocytes compared with patients of other glioblastoma subtypes. She hypothesizes that the vaccine is activating the immune response in these patients to fight the cancer.

The company recently resumed a randomized, double-blind Phase II pivotal study after a two-year hiatus due to funding, with 287 newly diagnosed patients who will receive the standard of care, surgery, temozolomide and radiation, and then vaccine every two weeks initially for three injections (on weeks 0, 2, and 4), or just the standard of care. Patients will then receive the vaccine every two months thereafter until tumor progression or vaccine runs out, whichever comes first.

Heat Shock Proteins
Instead of using dendritic cells to deliver tumor antigens, Agenus, Inc. uses heat shock proteins to act as a magnet for antigens, activating both CD4 and CD8 cells. Prophage, also known as vitespen, formerly HSPPC-96, is now in two Phase II trials. While previous trials with the vaccine in other cancers did not yield stellar results, one neurosurgeon who surveyed the landscape of possible new treatments for his glioma patients five years ago thought the vaccine had promise.

“Oncophage had merits that other therapeutics, such as dendritic cell treatments [not vaccines] and adoptive T cell therapies did not,” said Andrew Parsa, M.D., Ph.D., associate professor of neurosurgery at the University of California in San Francisco. Because heat shock proteins are potent immune activators, Parsa preferred using heat shock proteins over dendritic cells for a vaccine. Interested in testing ProPhage in his patients, Parsa obtained funding from the NCI and patient groups, and initiated two Phase I and Phase II investigator-sponsored trials. A Phase I trial in recurrent patients, reported in 2008 at the Society for Neuro-Oncology, showed an overall median survival of 10.5 months, with 4 living beyond 12 months, and one patient living at 2.5 years. Interim results from the Phase II trial in 2009 showed similar results: a median survival of 44 weeks, compared to the historical median of 26 weeks.

Dr. Lai has reported receiving research support and honoraria from Celldex Therapeutics.