Gene therapy increases survival for end-stage head and neck cancer

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A gene therapy invented at The University of Texas M. D. Anderson Cancer Center is the first to succeed in a U.S. phase III clinical trial for cancer, as announced today at the American Society of Gene Therapy annual meeting in Boston.

Introgen Therapeutics, Inc., reported results of its phase III trial of Advexin(r), a modified adenovirus that expresses the tumor-suppressing gene p53, for end-stage head and neck cancer.

"Cells become cancerous because p53 no longer functions. Restoring p53 works unlike any current cancer treatment because it treats the cancer genome," said Jack Roth, M.D., professor in M. D. Anderson's Department of Thoracic & Cardiovascular Surgery, who invented the drug and co-founded Introgen. He remains a shareholder and paid consultant to Introgen, and the University of Texas System is also a shareholder in Introgen.

The p53 gene is inactivated in many types of cancer. Its normal role is to halt the division of a defective cell and then force the cell to kill itself.

The trial showed that p53 expression in the patient's tumor before treatment is a reliable biomarker for how to treat head and neck cancer. Patients with a favorable p53 profile who received Advexin(r) had a median survival of 7.2 months, compared with 2.7 months for those whose tumor expressed high levels of mutant p53 before treatment. Patients with this unfavorable profile were better off taking the

chemotherapy drug methotrexate, resulting in median survival of 5.9 months.

"The important finding is that patients who benefit from treatment can be identified with the p53 biomarker. The biomarker will enable physicians to personalize treatment," said Roth, who also directs M. D. Anderson's W.M. Keck Center for Innovative Cancer Therapies.

Detailed results of the 123-patient clinical trial, led by John Nemunaitis, M.D., executive director of the Mary Crowley Medical Research Center at Baylor-Charles A. Sammons Cancer Center in Dallas, are available at www.introgen.com.

Better Quality of Life

Patients treated with Advexin experienced far fewer harmful side effects such as pneumonia than those who received methotrexate. The incidence of inflammation of the mouth lining and a decrease in white blood cells, for example, both dropped to zero for those receiving Advexin.

"That certainly results in a better quality of life," Roth noted, which makes sense because p53 does not cause problems in normal cells.

Roth's lab has been developing gene therapy for cancer since 1990. "We wanted to go beyond conventional treatment, because most of those treatments were not very effective," Roth said. "Surgery and radiation are limited to the local tumor and once given, it's very hard to repeat those therapies. Chemotherapy inhibits DNA replication, but it also interferes with normal cells."

All basic and preclinical work on the modified adenovirus was done at M. D. Anderson. The first phase I clinical trial was conducted by Gary Clayman, M.D., D.D.S., professor in M. D. Anderson's Department of

head and neck surgery. Clayman also enrolled patients in the phase II and phase III clinical trials conducted by Introgen.

Roth and colleagues deleted an important region of the adenovirus' genome, preventing it from replicating. They installed a genomic segment that expresses p53. When injected into a tumor, the p53 adenovirus burrows into the cancer cell's nucleus. But instead of replicating in a typical viral manner, it expresses p53, resulting in cell death.

Clayman's phase I trial provided the first indicator that p53 expression in the tumor before treatment could be an accurate biomarker for p53 therapy. The concept was further developed retrospectively in Introgen's phase II trial, Roth said, and then it was applied prospectively in the phase III trial, with results related to biomarker status blinded until final data analysis.

If a tumor expresses high or low levels of normal p53, or a very low level of mutant p53, conditions are favorable for Advexin. Tumors with high levels of mutant p53 do not respond well to p53-related therapy. The healthy and mutant p53 biomarkers are easily discerned with standard lab techniques, Roth said immunohistochemical staining detects protein levels, while gene chip analysis reveals gene sequence.

Creation of Introgen

Roth found little interest in gene therapy from established pharmaceutical companies, so in 1994 he co-founded Introgen working through M. D. Anderson's Office of Technology Management.

Introgen has since grown into a publicly traded company on NASDAQ, and while it still licenses important technology from M. D. Anderson, the company works broadly with other medical research institutions and

biotech firms.

Introgen developed a commercial-grade version of the drug and advanced it through phase II and III clinical trials for head and neck cancer. Advexin(r) also is being tested in other cancers in a variety of clinical trials.

"If something's going to get to patients, it has to be commercialized," Roth said. The National Cancer Institute funds basic and translational research but simply cannot afford to fund large, late-stage clinical trials, he said.

Nanotechnology and p53

Roth and colleagues now focus on ways to deliver p53 and other tumor-suppressing genes systemically - through intravenous delivery. Advexin has to be injected straight into the tumor, but that's not workable for many cancers. Head and neck cancer kills patients by recurring, not spreading to other organs, but most cancer deaths involve metastasis.

By wrapping tumor-suppressing genes in tiny balls of fat, Roth and colleagues hope to be able to treat more invasive cancers. While p53 nanoparticles are still in preclinical development, those that deliver another tumor-suppressor called FUS1 are in a phase I clinical trial for non-small cell lung cancer. Through 19 patients, the dose escalation study has yet to encounter significant side effects.

Injected nanoparticles gather mainly in tumors, where they are taken up and dissolved, leaving the tumor-suppressor gene at work in the cell. A version that combines FUS1 and p53 is under development.

Source: University of Texas M. D. Anderson Cancer Center