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Intravenous nanoparticle gene therapy shows activity in stage IV lung cancer

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A cancer-suppressing gene has been successfully delivered into the tumors of stage 4 lung cancer patients via an intravenously administered lipid nanoparticle in a phase I clinical trial at The University of Texas M. D. Anderson Cancer Center. The gene, FUS1, also was found to be active in the metastatic non-small cell lung cancer tumors.

"We've treated 13 patients in this first-in-human study and we've seen an exciting proof of concept with no significant drug-related toxicity," says principal investigator Charles Lu, M.D., associate professor in M. D. Anderson's Department of Thoracic, Head and Neck Medical Oncology.

Blinded analysis of pretreatment and post-treatment biopsies of three patients' tumors show that expression of FUS1 was absent from pretreatment samples while a high level of FUS1 was expressed in tumors after treatment. FUS1 can induce apoptosis - programmed cell death - in cancer cells but is frequently lost when normal cells become cancerous.

Lu presented a poster on the study on April 17 at the late-breaking abstract session of the American Association for Cancer Research annual meeting in Los Angeles.

Other attempts at gene therapy have employed an adenovirus to deliver the therapeutic gene. "Here we are using a non-viral, non-infectious delivery system," Lu says.

The only clinically significant side effect so has been fever, but Lu says premedication with a steroid and diphenhydramine has eliminated that so far.

Previous gene therapy clinical trials also involved direct injection into tumors. "This is the first time anyone has shown that a gene can be injected and then be taken up and expressed in cancer cells at distant sites," said Jack Roth, M.D., professor of the M. D. Anderson Department of Thoracic and Cardiovascular Surgery and a pioneer in the field of gene therapy.

FUS1 can induce apoptosis - programmed cell death - in cancer cells but is absent in those cells. The FUS1 nanoparticle formulation was developed and tested in Roth's lab. It advanced to phase I clinical trial after a promising test on human non-small cell lung cancer in a mouse model.

FUS1 was discovered by a research team led by Roth at M. D. Anderson and by John Minna, M.D., of the Department of Internal Medicine and Pharmacology, Hamon Center for Therapeutic Oncology Research, at The University of Texas Southwestern Medical Center at Dallas. Roth and Minna are the co-principal investigators of a National Cancer Institute Specialized Program of Research Excellence in Lung Cancer.

"As a clinician, I am very cautious about saying that we have shown clinical activity at this point. We have some encouraging data. The number of patients is too small to draw any definite conclusions, however," Lu said.

Three patients of eight who received two or more doses experienced stable disease for three to seven months. Median survival time for all patients is 14.6 months, which Lu notes compares favorably to a seven-month median survival time for patients receiving second line therapy.

All patients on the trial had been treated with front line cisplatin combination chemotherapy, which failed to halt their disease. The clinical trial continues. No maximum tolerated dose has been established, Lu says.

The nanoparticle delivery system consists of a plasmid gene expression cassette loaded with DNA that encodes the FUS1 protein. This is wrapped tightly in a form of cholesterol to protect it from the body's defense mechanisms. The nanoparticles accumulate mainly in the lungs, particularly in the tumors, where the genes repeatedly express FUS1 tumor-suppressing proteins.

Lung cancer is the leading cause of cancer death in the United States, causing 160,000 deaths annually. About 80 percent of lung cancer is of the non-small cell type.

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