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GENETICALLY ENGINEERED COLD VIRUS APPEARS TO KILL CANCER

AT A GLANCE

- A genetically engineered version of the cold virus can be safely injected into an artery to kill colon and other gastrointestinal cancers that have spread to the liver, a multi-center study shows.
- The therapeutic virus works like a new type of chemotherapeutic agent to kill cancer, but without harming healthy cells the way standard chemotherapy does.
- The virus is designed to infect only cancerous cells, killing them.
- Colon cancer kills 50,000 people every year, making it the third most deadly cancer.

BALTIMORE – Early research using a genetically engineered version of a common cold virus to treat colon and other gastrointestinal cancers that have spread to the liver is presented here today the 27th Annual Scientific Meeting of the Society of Cardiovascular & Interventional Radiology (SCVIR). Investigators in a multi-center study report that a therapeutic adenovirus, when injected into the artery leading to the liver, appears to kill tumors without harming healthy liver tissue.

Colon cancer kills 50,000 people every year in the United States, making it the third most deadly cancer. Colon cancer typically spreads to the liver, as do stomach, pancreatic and other forms of gastrointestinal cancer. Treatment options after spread to the liver include surgery and chemotherapy, but these benefit only a minority of patients.

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"You could think of this virus as a new generation of chemotherapy that is much more selective about what it attacks," said Daniel Y. Sze, M.D., Ph.D., assistant professor of radiology at Stanford University Medical Center, Stanford, Calif. "Standard chemotherapy kills some healthy cells along with the cancer. This engineered adenovirus is designed to kill only the cancer and not to harm healthy cells."

The therapy is genetically based, but is not gene therapy in the strictest sense. "Normally with gene therapy, a specific gene is spliced into a deactivated virus, and the virus acts as a 'vector,' a vehicle to get the gene inside the body's cells," said Dr. Sze. "In this case, we're using the live virus itself – without any extra gene – as the treatment. Rather than inject it directly into the tumor using a syringe and needle, where it might not get distributed evenly, we inject it into the artery, so that the flow of blood carries it throughout the liver, treating the entirety of each tumor." People with cancer that has spread to the liver typically have multiple tumors in the liver.

The synthetic virus is live, but is genetically engineered to be weaker, and therefore it is not as highly infectious as a normal cold virus. It was designed to infect only cells with an abnormality in the tumor suppressor gene, p53, which may be why those cells are susceptible to cancer to begin with, Dr. Sze said. P53 is part of the body's own surveillance system, which detects and destroys most early cancers. About one-half to two-thirds of cancers have abnormal p53 function.

Most patients feel sick with a mild flu for up to a week after the injection, although not as ill as they typically feel after standard chemotherapy, said Dr. Sze. Unlike most viruses used in gene therapy, this virus retains the ability to replicate, and because it copies itself, the virus is very effective at depleting the cancerous cell's resources and killing it. When the cancerous cell

dies, it breaks open and releases the virus and all its copies, which can then infect other cancerous cells and start the process again.

"The serendipitous finding was that although the lack of p53 makes a cell mean, aggressive and cancerous, it also can not recognize when it's been infected by a virus," said Dr. Sze. "That is its Achilles' heel: it makes the cell particularly susceptible to viral infection by this particular engineered virus."

The multi-center trial was conducted by multiple investigators at Stanford; Mayo Clinic, Rochester, Minn.; and M.D. Anderson Cancer Center, Houston. It was a dose-escalation Phase I trial, meaning its purpose was to determine whether the treatment is safe and what dose can be tolerated by patients. The trial included a Phase II extension, in which some patients were treated with a high dose. All 35 patients had gastrointestinal cancer – most originating in the colon – that had spread to the liver. Each had a life expectancy of approximately six months without this treatment. None were candidates for surgical removal of the liver tumor or tumors. Almost all had received chemotherapy, which was either unsuccessful or worked only temporarily.

After receiving the genetically engineered virus, none of the patients experienced toxic symptoms to the point where therapy needed to be stopped, even at the highest dose level. Dr. Sze said the results indicate the therapy is safe and research can progress to further Phase II efficacy studies.

Although a Phase I trial is designed to test for safety only, in this completed trial researchers found early evidence that the therapy does suppress tumors when it is administered in higher doses. The median survival time of the 28 patients who received the highest doses given in the trial was 369 days, about 1 year. The average expected survival time was approximately

180 days, or about 6 months. The suggestion of a beneficial effect will need to be proven in subsequent trials.

Computed tomography (CT) imaging showed that the tumors appeared to grow slightly larger immediately after the treatment, which was suspected to be an inflammatory response to the viral infection. The tumors then slowly got smaller.

"The tumors shrank somewhat, but more impressive was that blood tests showed that abnormal proteins being secreted by the tumors either decreased significantly, or became completely undetectable," said Dr. Sze. "That suggests the tumors, although still visible on the CT scan, are dying or dead."

In the Phase II study, due to start this year at the same institutions, investigators will treat cancer patients with the virus as well as chemotherapy to try to confirm the beneficial effects of the virus.

"This virus seems to have an additive affect with chemotherapy," said Dr. Sze. "It could be years before this treatment is ready for prime time, but it could eventually be a frontline therapy to treat various types of primary cancer, as well as tumors that have spread from the original site."

For his work, Dr. Sze was named winner of the Dr. Gary J. Becker Young Investigator Award by SCVIR.

An estimated 5,200 people are attending the SCVIR Annual Scientific Meeting in Baltimore. SCVIR is the professional society of interventional radiologists – physicians who specialize in minimally invasive, targeted treatments performed using imaging guidance.

Interventional radiology procedures are an advance in medicine that replace open surgical procedures. They are generally easier for the patient because they involve no large incisions, less risk, less pain and shorter recovery times. To find out more information about interventional radiology procedures or to find an interventional radiologist, visit the SCVIR Web site, www.scvir.org.

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