Researchers Formulate Treatment Combination Lethal To Pancreatic Cancer Cells (w/Video)

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A combination of two targeted therapies packs a powerful punch to kill pancreatic cancer cells in the laboratory, Mayo Clinic cancer researchers report. With further testing of these drugs that are from classes of pharmaceuticals already used in patients, the Mayo research may lead to new treatment opportunities for patients with pancreatic cancer, which is extremely difficult to treat.

In a study being presented at the annual meeting of the American Association for Cancer Research, Mayo Clinic Cancer Center investigators found that rapamycin and panobinostat (also known as LBH589) act synergistically when used in combination, destroying up to 65 percent of cultured pancreatic tumor cells.

The finding is particularly significant, says the study's first author, Mamta Gupta, Ph.D., because the three cell lines studied were all resistant to the effects of chemotherapy - as are many pancreatic tumors - and because the drugs studied are already available for treatment of patients. Panobinostat is approved as therapy for cutaneous T cell lymphoma (CTCL), and rapamycin is best known as an immunosuppressant to help prevent rejection of transplanted organs.

"We need new therapies and strategies for the treatment of pancreatic cancer because these tumors are resistant to almost all known treatments," says Dr. Gupta, a research associate in the Division of

Hematology. "No targeted treatment has shown much value to date."

Dr. Gupta studied the combination of agents in pancreatic cancer cells because her previous research at Mayo Clinic had shown that this combination worked well in laboratory tests of non-Hodgkin's lymphoma. A phase one clinical trial to test this combination in patients with lymphoma will open soon at Mayo Clinic under the direction of Thomas Witzig, M.D.

"While our pancreatic cancer cell line results look very promising, these are laboratory, not clinical, studies," she says. "We are preparing to take this combination of drugs to clinical trial to evaluate whether they can be safely given to patients."

While clinical studies will ultimately determine the benefits of panobinostat and rapamycin, Dr. Gupta and her colleagues remain focused on trying to understand the mechanism for how these agents together are so powerful.

Rapamycin and a closely related drug, everolimus (RAD001), have both been tested in pancreatic cancer cells, but by themselves have shown minimal activity, Dr. Gupta says. They belong to a class of agents known as mTOR inhibitors. The mTOR pathway is a major cellular survival mechanism that is persistently activated in pancreatic cancer cells.

In this study, rapamycin killed less than 5 percent of pancreatic cancer cells, and previous tests with RAD001 showed the same minimal effect, Dr. Gupta says.
Panobinostat is a histone deacetylase (HDAC) inhibitor. In cancer, HDAC proteins "silence" tumor suppressor genes, so an HADC inhibitor restores expression of these beneficial genes. The agent is also believed to block angiogenesis - the growth of new blood vessels needed for

tumors to grow," Dr. Gupta says.

Panobinostat killed about half of pancreatic cancer cells studied, she says. But both agents combined inhibited growth of pancreatic cancer cell lines and induced apoptosis (cell death) in up to 65 percent of the cells, Dr. Gupta says.

Dr. Gupta noted that panobinostat is effective at extremely low concentrations that are consistent with optimal pharmacological doses. "Our aim is always to use as little of a drug as possible in order to reduce potential side effects in patients," she says.

Although the researchers say they don't yet know the synergistic mechanism responsible for the combined drugs' effectiveness, they hypothesize that the agents are primarily interfering with the mTOR pathway, which is involved in growth and angiogenesis.

"Overall, these results indicate that rapamycin and panobinostat disrupts essential survival and proliferating pathways in pancreatic cancer cells, and this is a good start toward a novel treatment of this cancer," Dr. Gupta says.

Source: Mayo Clinic (news : web)