

New drug combinations may benefit patients with pancreatic cancer

October 21 2013

Two drug combinations that simultaneously block two major signaling pathways downstream of the protein KRAS, which is aberrantly active in most pancreatic cancers, may provide a new treatment option for patients with this disease, according to preclinical results presented here at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19-23.

Pancreatic cancer is one of the deadliest types of cancer, with a five-year survival rate of just 6 percent. Most pancreatic cancers harbor mutations in the KRAS gene. Because these mutations drive many of the cancerous characteristics of [pancreatic cancer](#) cells, the KRAS protein is a prime [therapeutic target](#). However, efforts to develop clinically useful drugs that block KRAS activity have been unsuccessful.

"KRAS has been a daunting therapeutic target," said Barry Nelkin, Ph.D., professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Md. "By combining drugs that simultaneously block two of the major signaling pathways triggered by KRAS, we have found a way to indirectly target this challenging protein.

"Our preclinical results were so positive that we have initiated a phase I clinical trial to evaluate one of the drug combinations, dinaciclib plus MK2206, in patients with pancreatic cancer."

In prior studies, Nelkin and colleagues found that an investigational drug

called dinaciclib had antitumor effects in mouse models of pancreatic cancer.

"Dinaciclib blocks the activity of a protein called CDK5, which is a key part of one of the signaling pathways that KRAS uses to exert its cancer-driving effects, the Ral pathway," explained Nelkin. "We wanted to investigate whether combining dinaciclib with a second drug that blocks one of the other signaling pathways triggered by KRAS would have even greater antitumor effects."

To conduct the study, Nelkin and colleagues used models of pancreatic cancer that closely resembled the human disease: They placed tiny pieces of human pancreatic tumors in the pancreata of mice and let them grow to about the size of a pea before beginning treatment.

The combination of dinaciclib and MK2206, which blocks the PI3K/AKT pathway triggered by KRAS, substantially inhibited [tumor growth](#) and reduced tumor spread to other parts of the body, a process called metastasis, compared with either drug alone. Further, when compared with no treatment, this drug combination reduced tumor growth by 90 percent, and in three of the 14 mice, no human pancreatic tumor tissue could be detected at the end of the experiment, indicating that there had been a complete response to the treatment.

The second drug combination tested—dinaciclib and SCH772984, which blocks the RAF/MEK/ERK pathway triggered by KRAS—also substantially inhibited tumor growth and reduced the number of metastases. It did not, however, lead to any complete responses.

The researchers are planning to investigate whether the drug combinations they used in this study can be further combined with current treatments for pancreatic cancer and if they can identify markers that might predict whether a given [pancreatic tumor](#) will respond to the

[drug combinations.](#)

More information: Abstract Number: B263

Presenter: Barry Nelkin, Ph.D.

Title: Combined inhibition of cyclin-dependent kinases (Dinaciclib) and AKT (MK-2206) or ERK (SCH772984) dramatically blocks pancreatic tumor growth and metastases in patient-derived orthotopic xenograft models

Pancreatic cancer is among the deadliest of all solid malignances. The 5-year survival rate of pancreatic cancer remains below 5%, mainly due to a lack of early detection and the highly metastatic properties that make surgery impossible in most cases. Therefore, it is urgent to find effective systemic therapies to treat this highly metastatic cancer. KRAS is activated in the vast majority of cases of pancreatic cancer; unfortunately, therapeutic attempts to inhibit KRAS directly have been unsuccessful. Our previous studies showed that inhibition of cyclin-dependent kinase 5 (CDK5), using genetic manipulation or the CDK inhibitor Dinaciclib, reduces pancreatic cancer growth and progression, through blockage of the Ral effector pathway, downstream of KRAS. Since Ral has been shown to be a centrally important effector of KRAS signaling in pancreatic cancer, we hypothesized that simultaneous blockage of two major downstream KRAS effectors may further inhibit the growth and metastasis of pancreatic cancer and provide an effective therapeutic strategy for this disease.

In the current study, the therapeutic effects of combining the CDK inhibitor Dinaciclib with inhibitors of either the PI3K/AKT effector pathway (pan-AKT inhibitor MK2206) or the RAF/MEK/ERK effector pathway (ERK inhibitor SCH772984) were evaluated using two orthotopic patient-derived human pancreatic cancer xenograft models (Panc253 and Panc265). These models closely resemble the

physiological and pathological conditions of pancreatic cancer in humans. A 2-3 mm³ tumor explant was implanted into the pancreas of nude mice and ultrasound imaging was used to measure the tumor size (3D) before randomization and treatment, which began when tumors grew to 50-100 mm³. The combination of Dinaciclib (20 mg/kg, i.p., t.i.w.) and MK2206 (60 mg/kg, p.o., t.i.w.) dramatically blocked tumor growth in the orthotopic Panc265 (90.0%, p

Citation: New drug combinations may benefit patients with pancreatic cancer (2013, October 21) retrieved 24 April 2024 from

<https://medicalxpress.com/news/2013-10-drug-combinations-benefit-patients-pancreatic.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.