Modified Vitamin D Shown to Make Pancreatic Cancer More Vulnerable to Chemotherapy

A synthetic derivative of vitamin D has been found by researchers at Salk Institute to collapse the barrier of cells shielding pancreatic tumors, making the "seemingly impenetrable" cancer much more susceptible to therapy.

By attacking the wound repair mechanism of fibrosis, the findings may also have implications for other difficult-to-treat tumors, such as lung, kidney and liver cancer, the senior author, Ronald Evans, PhD, a Howard Hughes Medical Institute investigator and Director of the Gene Expression Laboratory there, said in a news release.

"While the success of this drug in humans with pancreatic cancer is still unclear, the findings in animal studies were strong, raising hope that ongoing clinical trials will give people with this terrible disease hope for a truly new type of therapy."

Salk Institute

Evans Lab members and study coauthors (left to right): Ronald Evans, Mara Sherman, Ruth Yu, Ann Atkins, Tiffany Tseng, and Michael Downes.

SU2C Supported

The study, part of a Stand Up to Cancer-supported interdisciplinary initiative, is published in the Sept. 25 issue of Cell (***2014;159:80-93***).

continued on page 51

HONEY

Continued from page 49

during radiation and chemotherapy treatments.

The honey was donated to the trial by one of the Manuka honey distributors in New Zealand, Berk noted.

Patients kept a pain diary that helped determine swallowing pain as assessed on an 11-point scale at four weeks of radiation therapy—the primary endpoint of the study. That endpoint, though, he noted, was entirely arbitrary, and the researchers also tested a wide variety of secondary endpoints.

Standard of Care Is Individualized

Asked for his perspective for this article, Kenneth Roberts, MD, Professor of Therapeutic Radiology at Yale School of Medicine, said, "Standard of care for managing esophagitis is all individualized. We use a combination of local anesthetic agents, viscous lidocaine-containing mixtures, narcotic pain medicines, agents that reduce acid reflux, and agents that also coat the mucosa.

"But one of the major things we can do to reduce the risk of esophagitis is how we plan out the radiotherapy and being attentive to how much radiation goes to that organ, and then getting to patients to use these therapies to make patients more comfortable. If this particular type of honey had panned out, we would have had a very simple, non-toxic thing to use," he said.

Berk explained that although the trial had been foreseen as relatively straightforward, the project became subject to almost all the ills that can befall mankind, including an earthquake that shut down production of the product. The trial opened to accrual on February 28, 2012, and accrual was reached by October 15, 2013, despite being suspended twice.

A total of 53 patients were assigned to standard of care, 53 to receive liquid honey, and 54 to lozenge honey. Eventually, the researchers were able to evaluate the effects in 40 patients receiving best supportive care; 41 receiving liquid honey and 38 receiving lozenge honey.

The outcome: There were no differences between standard of care and liquid honey in numerical pain score, nor between the effects of lozenge honey and standard of care at four weeks.

In reviewing the multiple prespecified secondary endpoints, the researchers were able to observe one positive finding: Patients who were taking the lozenge reported a benefit in their numerical pain scores at 12 weeks.

"In the Radiation Trial Oncology Group, we are looking for ways to ameliorate the side effects of the treatments so we could reduce the dose of radiation," Berk said. "One area that is underexplored is radiation esophagitis. The other area of interest was natural products — the things that patients are interested in but generally aren't commonly investigated within the cooperative group trials."

He said that the trial might have had a different outcome if a different product had been selected to test. "We were dealing with natural products and I picked one, and it might have been the wrong product. Perhaps the product I selected did not have the appropriate active compound."

LAWRENCE BERK, MD, PHD: "The results from our study were somewhat unexpected since three previous trials had indicated that honey worked, and reducing esophagitis is important so that patients can continue eating their normal diet. Currently, honey cannot be recommended for every patient to use for esophagitis pain relief. However, it is safe and inexpensive, so if patients want to try it, there is probably little harm."

Roberts added that natural products are very difficult to study: "They are not standardized, and there are a lot of claims out there for all sort of different products. This was an attempt to pick one to see if it helped. It's a very benign agent to use, but it didn't show any benefit over standard of care."

PANCREATIC VITAMIN D

Continued from page 50

Evans explained that it has been known that the ability of the pancreatic tumor to communicate with nearby cells—i.e., the tumor microenvironment—is key to its growth. "Tumor cells send out signals that make the microenvironment inflamed and dense, and this 'living shield' around a tumor not only helps the cancer grow, but blocks the access of immune cells and chemotherapeutic drugs, making the cancer particularly hard to treat."

> "Instead of destroying the microenvironment to weaken the tumor, our approach is to reprogram the tumor microenvironment to a healthy state. This has the dual effects of delivering more drugs to the tumor as well as replenishing the tissue with normal stellate cells."

The hope was to discover how to restore this inflamed microenvironment to its normal, quiescent, state and weaken the wall around the tumor.

"There was evidence that the activation of the microenvironment was theoretically reversible, but nobody knew exactly what was responsible for the activation, making it hard to turn off," said the study's first author, Mara H. Sherman, a postdoctoral research fellow.

Pancreatic Stellate Cells

As explained in the news release, Sherman, Evans, and their collaborators focused on one component of this wall: pancreatic stellate cells, which usually respond to small injuries by briefly switching to an activated state, spurring new cell growth. In the case of cancer, however, the stellate cells near a tumor—in response to signals from the tumor—are constantly turned on.

This chronic activation provides the tumor cells with extra growth factors and helps them proliferate, but also forms a barrier around the tumor that protects it from chemotherapy.

Since previous research by Evans' group showed that stellate cells in the liver could be inactivated by a chemically modified form of vitamin D, the team wondered whether the same could hold true in the pancreas, despite the fact that the vitamin D receptor was not thought to be present in pancreatic tissue.

But when the differences between activated and inactivated stellate cells in the pancreas were investigated, it was found that activated stellate cells near a tumor had high levels of the vitamin D receptor. And when the researchers then added modified vitamin D to activated stellate cells, the cells quickly reverted back to a healthy, inactivated state, stopping production of signals that spur growth and inflammation.

'Big Surprise'

"This was a big surprise because vitamin D has been tried multiple times as a therapy for pancreatic cancer and never worked," Evans said.

It turns out that activated stellate cells rapidly break down normal vitamin D, preventing the vitamin from binding to the receptor, he continued. But systematic analysis of vitamin D analogues allowed the team to discover a modified form of vitamin D that is more stable, resilient, and effective in vitro.

The researchers found that combining this new vitamin D-like compound drug with existing chemotherapeutics in mice resulted in a 50 percent increase in lifespan compared with use of chemotherapy alone.

"It's really remarkable, considering that vitamin D itself is not attacking the cancer cells," said Michael Downes, PhD, a senior staff scientist at Salk and co-corresponding author of the study. "It's changing the environment to a more favorable setting needed for the chemotherapy drugs to work."

Evans said that studies have shown that people deficient in vitamin D are more likely to develop pancreatic cancer, and based on the new results, healthy levels of vitamin D may help keep vitamin D receptor signaling in stellate cells normal and squash a cancer's growth—at least until a tumor itself forces the stellate cells to turn on.

"Recently, other research groups have explored the idea of destroying the microenvironment to weaken a tumor," Downes said. "Our approach is very different. Instead of destroying, we simply want to reprogram the tumor microenvironment to a healthy state. This has the dual effects of delivering more drugs to the tumor as well as replenishing the tissue with normal stellate cells."

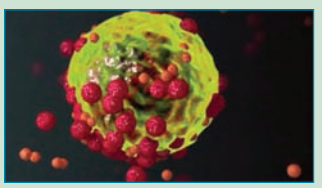
Clinical Trial

Evans' group has already teamed up with clinicians at the University of Pennsylvania to launch a clinical trial testing the effectiveness of using the vitamin D-like drug in cancer patients before pancreatic surgery. "Previous trials with vitamin D failed because they didn't understand the need for a special form of vitamin D and that for pancreatic cancer it must be used in combination with chemotoxic drugs," Evans said.

"So, by re-thinking the problem, we have been able to open up a new route to the treatment of pancreatic cancer and, looking forward, hopefully other diseases as well."

iPad Extra!

VIDEO: In this Salk Institute-created video, which can be seen on the iPad edition of this issue, **Ronald Evans, Mara Sherman**, and **Michael Downes** explain their work that found that a specially created vitamin D-derivative makes tumors more vulnerable to chemotherapy, suggestimg that use of "vitamin D priming" could be a useful addition to therapy for pancreatic ductal adenocarcinoma.



OT Video News

If you are not yet receiving our iPad issues, download the free Oncology Times app from the App Store today! Visit ***http://bit.ly/OT-iPadApp****, search in the App Store, or follow the link on* ***oncology-times.com****.*