Pancreatic cancer patients with BRCA mutation may benefit from targeted drug

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A physician-scientist at the University of Arizona Cancer Center investigated a novel treatment for pancreatic cancer patients whose tumors exhibited a harmful genetic mutation.

The results, in which a type of drug called a PARP inhibitor showed early promise in treating pancreatic cancer in patients with mutations in the BRCA gene, were published online last month in the *Journal of Clinical Oncology Precision Oncology*.

Rachna Shroff, MD, the UA Cancer Center's new section chief of gastrointestinal medical oncology and the study's principal investigator, said, "There are two combination chemotherapies that are approved for treating metastatic pancreatic cancer. Beyond that, not a lot has been proven to be successful in newly diagnosed patients."

Pancreatic cancer is predicted to become the second-deadliest cancer by 2020. In most cases, by the time the disease is diagnosed, the cancer has spread beyond the pancreas and cannot be cured with surgery. The cancer's deadliness is exacerbated by a dearth of treatment options.

Pancreatic cancer often is treated with a regimen called FOLFIRINOX, a combination that includes oxaliplatin, a platinum-based chemotherapy that blocks cell division. Tumors can develop resistance to platinum therapies, however, and when traditional chemotherapy fails, few options remain.

"The new frontier for pancreatic cancer is finding ways to target pancreatic cancer outside of traditional chemotherapy," Dr. Shroff said. Whereas chemotherapy drugs use a "wrecking-ball" approach to attack cancer cells without regard to their underlying genetics, cancer researchers hope for targeted treatments that can zero in like a laser on a tumor cell's unique molecular features. As genetic analysis becomes more widespread, scientists could begin to identify different subsets of pancreatic cancers, each of which could be targeted by drugs optimized for their unique genetic profiles.

Nine percent of pancreatic cancer patients have a mutation in the BRCA gene, making them one subset that already has been identified. Under normal circumstances, BRCA keeps tumors at bay by repairing damaged DNA. However, a mutation in BRCA causes it to lose its tumor-suppressing abilities, increasing susceptibility to cancer.

"This is a very important subset," said Dr. Shroff. "I don't think we've fully understood how best to serve this population."

PARP is a protein that repairs damaged DNA in tumor cells, helping cancer to grow. Rucaparib is a PARP inhibitor, a drug that blocks PARP from repairing DNA, thereby killing cancer cells. Because it is effective in breast and ovarian cancers with the BRCA mutation, Dr. Shroff hoped to learn if it would work in pancreatic cancer patients with that mutation as well.

"Cancer cells are rapidly dividing," Dr. Shroff explained. "This inhibitor targets the enzyme that helps them rapidly divide and grow without errors in DNA replication. PARP is probably one of the few valid targets we have identified in pancreatic cancer."

The study, which Dr. Shroff led when she was at MD Anderson Cancer Center, was one of a small handful looking at the efficacy of PARP inhibitors in pancreatic cancer patients with the BRCA mutation. A total of 19 patients were enrolled. Participants had locally advanced or metastatic pancreatic cancer, and had only received one or two previous chemotherapy regimens. Some of these patients saw results. "Patients who did respond responded nicely and for a while," reported Dr. Shroff. "We had one complete response—the disease completely melted away."

Overall, 32 percent of patients experienced disease control, in which tumors either stopped growing, got smaller or disappeared. Among patients who only had received one previous chemotherapy regimen, 44 percent experienced disease control.

The fact that patients with less exposure to chemotherapy were more likely to respond to PARP inhibitors indicates that tumor cells that acquire the tools to resist platinum-based drugs also could have the skills needed to resist PARP inhibitors.

"As we started to think about the 'would have, could have, should haves,' we thought perhaps the way to design the study would be in patients who were platinum-sensitive," said Dr. Shroff.

Despite the small sample size, investigators concluded that PARP inhibitors such as rucaparib could help the subset of pancreatic cancer patients with BRCA mutations, especially those whose diseases did not worsen when on platinum-based therapy.

"This study paves the way for further studies with PARP inhibitors in patients with advanced pancreatic cancer and alterations in the BRCA pathway," said Dr. Shroff. "It was one of the landmark studies looking at this therapy in BRCA-mutated pancreatic cancer only."

Although current research into PARP inhibitors focuses on these drugs when used alone, Dr. Shroff believes they might be better when combined with other treatments. She hopes to design trials to test the efficacy of PARP inhibitors with immunotherapy, drugs that train the body's immune system to recognize and attack cancer cells.

"Pancreatic cancer is a devastating disease with very poor survival in advanced stages," said Dr. Shroff. "It is now the third-leading cause of cancer death in the United States. Finding new treatment options is crucial."

More information: Rachna T. Shroff et al. Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation, *JCO Precision Oncology* (2018). DOI: 10.1200/PO.17.00316

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