Combining Chk1 inhibition with standard dose Gemcitabine may be safe and effective

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Adding the investigational agent GDC-0425, which blocks the function of a protein called checkpoint kinase 1 (Chk1), to standard doses of the chemotherapy drug gemcitabine, was safe and yielded responses in patients with a variety of cancer types, including triple-negative breast cancer, melanoma, and cancer of unknown primary, according to data from a phase I clinical trial presented at the AACR Annual Meeting 2015, held April 18-22.

"Gemcitabine is a chemotherapy agent that works by damaging the DNA of cancer cells while they are dividing to form more cancer cells," said Jeffrey R. Infante, MD, director of the drug development program at Sarah Cannon Research Institute in Nashville, Tennessee. "Sometimes cancer cells pause during the process of cell division and the cell has time to repair the DNA damage caused by gemcitabine, making the drug less effective. Chk1 is a protein kinase that can trigger this pause, and the idea underpinning our trial was that blocking Chk1 with GDC-0425 might prevent cancer cells from having time to repair gemcitabine-damaged DNA.

"We were excited to find that we could safely combine GDC-0425 with the standard 1000 milligram per m2 dose of gemcitabine because we had been concerned that this combination might not be tolerable," continued Infante. "We are also encouraged to see responses in patients with a variety of cancer types. The results have given us a good platform for moving forward with Chk1 inhibitor/gemcitabine combination therapy for further study."

Infante and colleagues enrolled 40 patients with a variety of cancer types in the dose-escalation clinical trial, including 10 patients with breast cancer, five patients with non–small cell lung cancer, and three patients each with cancer of unknown primary and melanoma. They found that the maximum-tolerated dose of the combination was 60 milligrams of GDC-0425 with 1000 milligram per m2 gemcitabine. The most frequent adverse events were nausea, anemia, neutropenia, vomiting, fatigue, fever, and thrombocytopenia.

Among the 40 patients on the trial, three experienced partial responses to the drug combination. One patient with triple-negative breast cancer had a partial response that lasted more than 10 months, and two patients, one with melanoma and one with cancer of unknown primary, had partial responses that lasted more than 7.5 months.

Infante said that the researchers analyzed archival tumor samples from the patients enrolled on the clinical trial for mutations in the gene TP53, which is the gene most frequently mutated in human cancers. "The idea is that TP53 mutations may make a tumor more responsive to Chk1 inhibitor/gemcitabine combination therapy," he said. "Unfortunately, we did not have enough data from the dose escalation portion of the study to confirm whether TP53 mutations are a biomarker of response, but this is an important question that will need to be addressed in future trials."

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