New inhibitor prevented lesions, reduced tumor size in basal cell cancer

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A new hedgehog pathway inhibitor demonstrated efficacy in preventing and treating basal cell cancer among patients with basal cell nevus syndrome, a rare inheritable disease, according to Phase II data presented at the AACR 102nd Annual Meeting 2011, held April 2-6.

In 1996, Ervin Epstein Jr., M.D., senior scientist at Children's Hospital of Oakland Research Institute, and colleagues identified the site of the mutation that causes basal cell nevus syndrome: the PTCH gene, which encodes a primary inhibitor of the hedgehog signaling pathway. This pathway provides information for the proper development of an embryo; when the pathway malfunctions in adulthood it can produce basal cell carcinomas, the most common human cancer.

Using this information, researchers developed GDC-0449, which Epstein said "is the first drug in man that is an anti-hedgehog signaling pathway drug."

"These data are a triumph for the idea that if you really understand the fundamental flaw in cancer, you can attack it in a much more specific way and avoid side effects of the more traditional chemotherapy," he said.

Phase I data have shown that GDC-0449 reduced locally advanced/metastatic basal cell carcinomas. For this randomized, double-blind, placebo-controlled trial, the researchers enrolled 41 patients who had basal cell nevus syndrome. They randomly assigned patients to

receive 150 mg GDC-0449 or placebo.

During the interim analysis, the data safety monitoring board stopped the placebo arm of the trial because of statistically significant differences between patients receiving GDC-0449 and those receiving placebo. Those patients treated with GDC-0449 developed 0.07 new basal cell carcinomas per month compared with 1.74 new basal cell carcinomas per month among those who recieved placebo. The size of existing basal cell carcinomas decreased significantly in the GDC-0449 group but was essentially unchanged in the placebo group.

None of the patients who received GDC-0449 required surgical removal of any basal cell carcinoma (BCC) during the course of the study — a significant finding for these patients who can develop many lesions that require surgical removal multiple times a month.

"These tumors disappear completely; all of them have vanished after somewhere between six and 12 months," Epstein said. "There's an immediate diminution that you can recognize after one or at most two months of treatment, and so far we have not seen any BCC that developed resistance to the drug."

Common side effects included loss of taste, muscle cramps and weight loss. Two patients experienced grade 3 to 4 adverse events including muscle cramps as well as a suicide attempt in one patient who made two such attempts prior to beginning study medication. Twenty percent of patients discontinued GDC-0449 because of side effects.

Although the researchers hope to use GDC-0449 and other hedgehog inhibitors vs. single sporadic BCC tumors eventually, Epstein explained that it may be impractical for a patient with a single tumor to endure the side effects of these inhibitors when they have small single lesions that can be removed surgically.

"In the regimen given, it's unlikely that GDC-0449 would be adopted for many patients with sporadic basal cell carcinomas," Epstein said. "But clearly our findings indicate that basal cell carcinomas are highly susceptible to this drug, and with different delivery and different dosing, perhaps some of these lesions might be eventually treated with such chemical entities as opposed to surgery."

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