

Novel anti-cancer drug yields positive response in people with advanced skin, brain cancer

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The Hedgehog signaling pathway is involved in a preliminary study and case report describing positive responses to an experimental anticancer drug in a majority of people with advanced or metastatic basal cell skin cancers. One patient with the most common type of pediatric brain cancer, medulloblastoma, also showed tumor shrinkage.

Initial results of the drug trial, conducted at Johns Hopkins (Baltimore), the Karmanos [Cancer](#) Center (Detroit) and the Translational Genomics Research Institute (Scottsdale) are published online September 3 in the [New England Journal of Medicine](#) (*NEJM*). The publication also details side effects of the drug, including muscle cramping, hair loss, fatigue and low blood sodium.

The compound, known as GDC-0449, is designed to inhibit the Hedgehog signaling pathway, thought to fuel growth of some cancers. The pathway was originally named for the oblong hedgehog like shape of fly embryos when a key gene in the pathway is disrupted.

Related research by Johns Hopkins and Genentech investigators reported online in the September 3 issue of *Science Express* reveals more findings on the medulloblastoma case.

"We know that both of these cancer types have mutations in Hedgehog pathway genes, and our results with Hedgehog inhibitors could be the

starting point for developing a new type of therapy for these intractable cancers," says Charles Rudin, M.D., Ph.D., associate director for Clinical Research at the Johns Hopkins Kimmel Cancer Center.

In the Phase I clinical study, 33 patients with advanced basal cell [skin cancer](#) were treated with GDC-0449, an oral drug made by Genentech. Patients were enrolled at Johns Hopkins, Wayne State University's Karmanos Cancer Center, and the Translational Genomics Research Institute.

Of the 33, 18 had metastatic disease spread to other organs, and 15 had locally advanced disease at the original tumor site. Half of the patients with metastatic cancer responded to the therapy as measured by tumor regression of 30 percent or more. Nine of the 15 patients with local recurrences also responded to the drug. The remaining patients had either stable or progressive disease at a median of nearly 10 months follow-up.

Analysis of patients' skin biopsies revealed that the drug inhibited the Hedgehog signaling pathway.

Rudin and his team also gave the drug to one patient with advanced medulloblastoma, as described in a separate case report in *NEJM*. The patient, whose cancer recurred 18 months after initial surgery and treatment, had tried several additional therapies with no success. Investigators found that samples of his tumor had very high levels of activity in the Hedgehog pathway.

"Within a few weeks of the treatment, the drug had a remarkable effect on the patient," says Rudin. "He went from being nearly bedridden with significant pain to exercising and having no pain." Rudin recounts that the patient's tumor began to regress, and he gained weight and his requirements for blood transfusion improved. Two months later,

however, the cancer progressed and drug treatment could not be sustained. He subsequently died.

Additional research, published online in the Sept. 3, 2009, issue of *Science Express* by investigators at Johns Hopkins and Genentech, focuses on how the medulloblastoma tumor became resistant to the Hedgehog inhibitor. When the cancer recurred, it had acquired a mutation in a gene known as SMO, which encodes the target of the Hedgehog inhibitor drug. This mutation prevents GDC-0449 from binding to its target. In a mouse model of medulloblastoma selected for GDC-0449 resistance, the researchers found a mutation in the very same location in the mouse SMO gene.

Research over the past several years has shown that mutations in genes encoding a family of proteins known as tyrosine kinases are important causes of relapse in cancer patients treated with other targeted cancer therapies, including in lung cancer patients treated with erlotinib. Mutations in SMO, like the one found in this patient, may similarly be an important cause of resistance to Hedgehog inhibitors, says Rudin. Researchers are now evaluating strategies for treating cancers with acquired resistance, to try to maintain the initial good responses seen in some patients treated with these drugs.

The Hedgehog gene got its name from scientists who first studied it in fruit flies. In humans, the Hedgehog pathway has long been known to contain genes that control fetal development and cell growth, and when altered, the pathway can cause excessive cell growth, a hallmark of cancer.

Investigators have begun a clinical trial of GDC-0449 at several U.S. cancer centers for children with medulloblastoma. The disease is typically treated with surgery, radiation and chemotherapy, which can have severe side effects. When it recurs, the cancer is often fatal.

Basal cell skin cancers are the most common type of cancer in adults and are often cured with surgery. It spreads in the body in a very small percentage of people. There are no chemotherapy drugs proven effective in treating metastatic basal cell cancer.

Source: Johns Hopkins Medical Institutions

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