Oral anti-fungal drug can treat skin cancer in patients

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(Medical Xpress)—Decades of research and millions of dollars go into developing new cancer drugs from scratch. But what if the next cure is a pill that's already tucked away in a bottle at the local pharmacy?

One such drug, a common anti-fungal treatment called itraconazole, may be useful in treating basal cell carcinoma—the most common form of skin cancer, according to a study that was published online Feb. 3 in the *Journal of Clinical Oncology*.

The study tested itraconazole's effectiveness in treating patients with multiple basal cell carcinoma tumors. Researchers at the Stanford University School of Medicine carried out a phase-2 clinical trial with 29 patients who had a total of 101 tumors. Within a month, the size and spread of tumors had decreased in most patients, they found.

Basal cell carcinoma affects nearly 3 million people in the United States every year. Triggered mainly by excess sun exposure, it is rarely fatal, but advanced-stage tumors can cause pain and skin disfigurement. Older adults with light skin are particularly at risk.

The study describes the first evidence of itraconazole's usefulness in treating this type of skin cancer. It also demonstrates how an existing drug can be repurposed to treat cancer, said Jean Tang, MD, PhD, associate professor of dermatology and the senior author of the study. Daniel Kim, a graduate student at Stanford, is the lead author.

"New drugs cost about $800 million and an average of 10 years to develop," Tang said. "We are shortcutting the process by using a drug that's already been around for 25 years and given to tens of thousands of people."

Itraconazole, which is prescribed for common fungal infections, kills fungal cells by blocking the production of a vital membrane component. In cancer cells, the drug appears to disable the Hedgehog signaling pathway—a cascade of cellular events triggered by the Hedgehog protein signal that is vital to cell growth and development.

The Hedgehog pathway was first identified for its role in controlling how the fruit fly's body is divided into segments. Fly embryos lacking the pathway's key protein messenger resembled spiny hedgehogs. Proteins in the pathway relay vital signals for cells to grow and divide in embryos and tumors. In healthy adult cells, the pathway is mostly involved in maintaining and repairing tissues. It also plays a role in regulating how stem cells generate different cell types.

Researchers previously showed that mice with improperly activated or absent Hedgehog proteins can develop cancers and deformed vital organs.

For the current study, Tang teamed up with co-author Philip Beachy, PhD, professor of biochemistry and of developmental biology, who has been studying the Hedgehog signaling pathway for many years.

In 1998, Beachy's lab identified the first known inhibitor of the Hedgehog pathway—a plant compound called cyclopamine—as well as several chemical alternatives. But they knew that developing commercial drugs to target the hedgehog pathway from scratch could be a tedious and financially risky process.

Four years ago, Beachy, along with then-postdoctoral scholar James Kim, MD, PhD, published a study identifying drugs that had already been approved by the Food and Drug Administration, or previously tested in clinical trials, that could block the Hedgehog pathway. Kim is also a co-author of the current study.

"We realized that if there are drugs already out there with the potential, it would be much easier to bring them to patients," said Beachy, who is also the Ernest and Amelia Gallo Professor in the School of Medicine.

Some of the 2,400 drugs they screened showed potential. But itraconazole was the most promising because it could block the Hedgehog pathway at the normal dosage prescribed for fungal infections. Mice treated with itraconazole showed greatly reduced tumors.

Tang then carried out the first set of clinical trials, and those findings are reported in the new paper. Patients were given itraconazole pills twice a day for a month. Another small group was given a lower dosage of itraconazole for a longer duration (an average of 10 weeks).

In the first group, the drug reduced Hedgehog pathway activity by an average of 65 percent and tumor size by 24 percent. Patients in the second group, with lower itraconazole doses, showed similar reductions in tumor size.

"The next step is to test itraconazole in more patients for a longer time to really measure its anti-tumor effect relative to other treatments," Tang said. Side effects of itraconazole (sold under the brand name Sporanox) are generally mild and include nausea, fatigue and dizziness. In rare cases, it can cause liver dysfunction. Patients with congestive heart failure or a history of heart disease are not advised to take itraconazole.

Tang's previous work focused on clinical trials of vismodegib, the first FDA-approved basal cell carcinoma drug tailored to shut down the Hedgehog pathway. Vismodegib was found to be highly potent and is currently considered the first line of treatment for advanced basal cell carcinoma tumors. But the drug took years to discover and develop, and a yearlong prescription costs patients about $90,000—or roughly $250 a day.

Although itraconazole does not appear as effective as vismodegib on advanced tumors, it may potentially treat smaller tumors and is much less expensive, costing about $20 a day.

"An interesting feature of itraconazole is that it can inhibit cancer cells that have developed resistance to vismodegib or other cancer drugs that block the Hedgehog pathway," Beachy said. "It may work better as an alternative treatment or in combination with other treatment options."

Tang is now working on clinical trials testing a combination of itraconazole and arsenic trioxide in patients resistant to vismodegib treatment.

More information: "Open-Label, Exploratory Phase II Trial of Oral Itraconazole for the Treatment of Basal Cell Carcinoma." Daniel J. Kim, James Kim, Katrina Spaunhurst, Javier Montoya, Rita Khodosh, Kalyani Chandra, Teresa Fu, Anita Gilliam, Monserrat Molgo, Philip A. Beachy, and Jean Y. Tang. *JCO*, published online on February 3, 2014; DOI: 10.1200/JCO.2013.49.9525

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