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Novel approach for estrogen-receptor-positive breast cancer reported

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Loyola researchers and collaborators have reported promising results from a novel therapeutic approach for women with estrogen-receptor-positive breast cancer.

The new approach, a new drug class called gamma secretase inhibitors (GSI), specifically inhibits Notch and shuts down critical genes and cancer cells responsible for tumor growth.

Kathy Albain, MD, FACP, who led the study, will present findings Dec. 11 during the 2014 San Antonio Breast Cancer Symposium.

Existing cancer drugs are effective in killing mature breast cancer cells. But a handful of immature breast cancer stem cells are resistant to such drugs. They survive and are responsible for tumor growth and progression. Resistance to standard therapy is a major cause of death in women with estrogen-receptor-positive breast cancer. Approximately 75 percent of breast cancers are estrogen-receptor positive.

"New treatments are desperately needed for women with estrogen-receptor-positive breast cancer who develop resistance to standard therapies," said Dr. Albain, a professor in the Department of Medicine, Division of Hematology/Oncology at Loyola University Chicago Stritch School of Medicine. "Our research suggests a potential role this new experimental drug class may have in optimizing existing endocrine therapies, such a tamoxifen and aromatase inhibitors, and in overcoming resistance to cancer drugs."

The Notch protein promotes tumor growth and survival. The protein is present on the surface of cancer stem cells. The protein latches on to other cells, and the resulting "molecular handshake" activates various genes in the stem cells that drive tumor growth, spread and survival. Activating these genes, in effect, makes the stem cells resistant to common cancer drugs. A pilot study conducted at Loyola found that the GSI appears to block this process by turning off key genes.

The purpose of the study was to identify critical genes involved in the process. The study included 20 patients with early-stage, estrogen-receptor-positive breast cancer. Prior to surgery, the patients received one of two commonly used drugs, tamoxifen or letrozole, for 14 days to block the estrogen stimulation of breast cancer cells. They underwent a biopsy on day 14. They then received the GSI, MK-0752, plus continued one of two standard drugs, tamoxifen or letrozole. Patients underwent their definitive breast cancer surgery on day 25 and part of this tumor was provided as well for this research.

Researchers discovered 18 genes that are regulated by Notch and are significantly reversed by the addition of the GSI, even though it was a very short exposure. They also identified a gene called DAXX that is critical for stem cell survival, which was turned off by the GSI.

"Identifying these genes may help us predict which patients will respond well to the GSI anti-Notch therapy," said Dr. Albain, who also is a medical oncologist and co-leader of Loyola's Breast Cancer Research Program.

There were minimal side effects reported in this study from either the GSI or the hormone therapy. One patient experienced puffy eyes and coughing and four patients experienced facial acne. No patients experienced diarrhea or surgical complications.

Researchers are planning a larger, phase II study to evaluate the efficacy of the GSI class of drugs added to endocrine therapy versus endocrine therapy alone. This study also will determine how well the 18 gene "signature" will predict who responds to therapy.

"This is an exciting new strategy to overcome resistance to a very common class of drugs (tamoxifen, letrozole), so it is our hope that in the future a vast number of patients with estrogen-receptor-positive breast cancer could benefit," Dr. Albain said.

Provided by Loyola University Health System