Medical Xpress

Experimental breast cancer drug holds promise in combination therapy for Ewing sarcoma

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Ewing sarcoma tumors disappeared and did not return in more than 70 percent of mice treated with combination therapy that included drugs from a family of experimental agents developed to fight breast cancer, reported St. Jude Children's Research Hospital scientists. The study will appear in the November 6 edition of the scientific journal *Cell Reports*.

The treatment paired two chemotherapy drugs currently used to treat Ewing sarcoma (EWS) with experimental drugs called poly-ADP ribose polymerase (PARP) inhibitors that interfere with DNA repair. PARP inhibitors are currently in clinical trials for the treatment of certain breast and ovarian cancers as well as other solid tumors. EWS is a cancer of the bone and soft tissue that strikes primarily adolescents and young adults.

A clinical trial using the three-drug combination therapy detailed in this research is expected to open later this year for adolescents and young adults with EWS whose tumors have not disappeared with standard therapy or have returned after treatment. The trial is a collaboration of researchers at St. Jude and the Dana-Farber/Harvard Cancer Center in Boston. The therapy will pair the PARP inhibitor olaparib with the chemotherapy drugs irinotecan (IRN) and temozolomide (TMZ).

The study is one of two clinical trials St. Jude plans to open soon combining IRN and TMZ with PARP inhibitors for the treatment for

EWS. The tumor is diagnosed in about 250 U.S. residents each year, making it the second most common bone tumor in children and adolescents.

Long-term survival for EWS patients whose disease has not spread remains stalled at about 75 to 80 percent, and the outcome for patients with metastatic disease is dismal. "During the past 20 years there has been no significant improvement in the cure rate for Ewing sarcoma, and survival is just 15 to 20 percent for patients whose disease has spread or comes back after treatment," said co-corresponding author Michael Dyer, Ph.D., a Howard Hughes Medical Institute (HHMI) investigator and a member of the St. Jude Department of Developmental Neurobiology. The other corresponding author is Anang Shelat, Ph.D., an assistant member of the St. Jude Department of Chemical Biology and Therapeutics.

This study builds on earlier research from other investigators who reported that EWS cells growing in the laboratory were sensitive to the PARP inhibitor olaparib. A clinical trial of olaparib for treatment of adults with EWS that had spread or returned opened a short time later.

The latest report includes the St. Jude discovery that EWS cells have a defect in DNA damage repair. DNA is the molecule contained in nearly every cell that carries the instructions needed to assemble and sustain life.

Working with EWS cells grown in the laboratory and mice, investigators showed the EWS defect could be exploited to help patients by combining DNA-damaging chemotherapy with a PARP inhibitor. PARP inhibitors work by interfering with activity of an important DNA-repair enzyme.

St. Jude researchers conducted a series of mouse experiments designed

to mirror the human phase I, II and III studies that gauge the safety and effectiveness of experimental treatment in humans. The research showed that PARP inhibitors work synergistically with IRN and TMZ to kill EWS. The Phase III study included 274 mice with EWS treated in a double-blind, placebo controlled, randomized study. The study included 15 different treatment groups using different combinations and doses of IRN, TMZ and three PARP inhibitors currently in development for pediatric cancer treatment.

EWS disappeared and had not returned in more than four months in 71 percent of mice treated with IRN, TMZ and the PARP inhibitor olaparib. The results were even better when IRN and TMZ were combined with the PARP inhibitor talazoparib. The combination led to a durable, complete remission in 88 percent of the 16 mice treated.

"Our preclinical results suggest Ewing sarcoma is particularly sensitive to this combination therapy, a possible indication that the tumor's DNA repair defect provides us with a much needed advantage to knock out tumor cells," Shelat said. "There is some evidence that this type of defect is present in other pediatric tumors, and we are actively investigating drug sensitivity in those cancers."

Researchers used the low-dose, protracted IRN treatment schedule pioneered at St. Jude to reduce IRN toxicity. Adult cancer patients receive fewer, but higher doses of IRN. The adult treatment regimen led to higher toxicity in mice. "The only way to move forward was using the irinotecan approach proven in earlier St. Jude solid tumor clinical research," Dyer said.

One of the planned St. Jude-led clinical trials will combine talazoparib and IRN for the treatment of patients age 1 and older. The other will involve triple drug therapy for treatment of patients age 16 and older.