MedicalXpress

PARP inhibitors may have clinical utility in HER2-positive breast cancers

September 17 2012

Poly (ADP-Ribose) polymerase (PARP) inhibitors, shown to have clinical activity when used alone in women with familial breast and ovarian cancers linked to BRCA mutations, may be a novel treatment strategy in women with HER2-positive breast cancers, according to the results of a study published in *Cancer Research*, a journal of the American Association for Cancer Research.

Currently, women with HER2-positive breast cancers are treated with therapies that target HER2. However, many women with this form of cancer either fail to ever respond to these targeted therapies or initially respond to them but then become resistant to their effects.

"Until now, PARP inhibitors have been shown to exhibit single agent activity only in tumors that are deficient in DNA repair, such as familial breast and ovarian cancers that are linked to BRCA mutations," said Eddy S. Yang, M.D., Ph.D., assistant professor in the department of radiation oncology at the University of Alabama-Birmingham.

According to Yang, only about 5 to 10 percent of all breast and ovarian cancers are BRCA-associated familial cancers, so researchers are currently trying to expand the patient population that might benefit from PARP inhibitors, which are generally well tolerated and have relatively few side effects.

"To do that, we were attempting to render nonfamilial cancers deficient in DNA repair," he said.

In prior studies, the Yang lab found that inhibiting the epidermal growth factor receptor (EGFR) pathway, which is commonly overactive in many tumor types, resulted in a DNA repair defect similar to that seen in familial cancers. They subsequently showed that this "forced" DNA repair defect increased tumor sensitivity to PARP inhibitors. Because HER2 and EGFR are in the same family of proteins, Yang and colleagues theorized that HER2-targeted therapies might force a similar DNA repair defect in HER2-positive tumors, increasing their sensitivity to PARP inhibitors.

They found that HER2-positive breast cancer cell lines were indeed sensitive to PARP inhibitors, both in culture and when transplanted into mice.

"However, the surprise was that these HER2-positive tumors were sensitive to PARP inhibitors alone, independent of a DNA repair defect," Yang said. "This means that there may be other mechanisms, outside of DNA repair, that dictate the sensitivity of a tumor to PARP inhibitors."

The researchers hope to further map out the reason why HER2-positive tumors are sensitive to PARP inhibitors. If better defined, the knowledge could ultimately broaden the clinical application for PARP inhibitors.

"Our research suggested that inhibition of NF-kB signaling is a possible cause of this sensitivity, but there may be other determinants as well," Yang said. "If we are able to find the determinants of sensitivity, we may be able to extrapolate our effects to other tumor types."

Provided by American Association for Cancer Research