Experimental drug inhibits cell signaling pathway and slows ovarian cancer growth

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An experimental drug that blocks two points of a crucial cancer cell signaling pathway inhibits the growth of ovarian cancer cells and significantly increases survival in an ovarian cancer mouse model, a study at UCLA's Jonsson Comprehensive Cancer Center has found.

The drug, called NVP-BEZ235, also inhibits growth of ovarian cancer cells that have become resistant to the conventional treatment with platinum chemotherapy, and helps to re-sensitize the cancer cells to the therapy. It also enhances the effect of platinum chemotherapy on ovarian cancer cells that are still responding to the therapy, said Dr. Oliver Dorigo, an assistant professor of obstetrics and gynecology, a Jonsson Cancer Center researchers and senior author of the study.

"Platinum-based chemotherapy drugs are effective in treating ovarian cancers as long as the cancer cells remain sensitive to platinum," Dorigo said. "But once the tumor becomes resistant, treating the cancer becomes very challenging. This is a significant clinical problem, since the majority of ovarian cancer patients develop resistance at some point during treatment. Breaking chemotherapy resistance is a difficult challenge, but crucial if we want to improve long-term survival for our patients."

The study, performed on cells lines and mouse models, appears in the April 15, 2011 issue of the journal *Clinical Cancer Research*.

Dorigo has been working in his laboratory over the last several years in

an effort to develop new therapies for ovarian cancer. About 22,000 American women are diagnosed with ovarian cancer, and more than 14,000 deaths are attributed to this disease every year. Dorigo has focused his research efforts on a pathway called PI3Kinase/Akt/mTOR, which once activated promotes ovarian cancer growth. The activated pathway also makes the cancer more aggressive and more likely to spread to other organs, Dorigo said, so targeting it offers great promise for more effective therapies for the disease.

In this two-year study, Dorigo and postdoctoral fellow Chintda Santiskulvong found that inhibiting two checkpoints of the pathway - PI3Kinase and mTOR - with NVP-BEZ235 decreased cancer growth, both in cell culture dishes and in mice with ovarian cancer. It also significantly increased survival in the mice, he said. More importantly, NVP-BEZ235 slowed growth of the ovarian cancer cells that had become resistant to platinum and helped to break that resistance.

"We were very encouraged to find that NPV-BEZ235 could re-sensitize the ovarian cancer cells to standard platinum treatment," Dorigo said. "In addition, we found this drug to be more effective in inhibiting ovarian cancer cell growth than other drugs that target only one checkpoint, mTOR, in this pathway. We believe that NVP-BEZ235 has superior efficacy because of the dual effect on PI3Kinase and mTOR."

The experimental drug is being tested as a single agent at the Jonsson Cancer Center in human clinical trials against other solid tumors. Researchers involved with those studies have said early results are encouraging.

"This is clearly a promising agent with activity in humans," said Dr. John Glaspy, a professor of hematology/oncology and a Jonsson Cancer Center scientist involved with the studies. "We are still assessing its tolerability in patients."

Dorigo said he hopes to initiate a clinical trial for women with ovarian cancer that tests the combination of NVP-BEZ235 with platinum chemotherapy, as he believes that the combination might be more effective than each drug alone. .

Provided by University of California - Los Angeles