Antihypertension drug losartan may improve treatment of ovarian cancer

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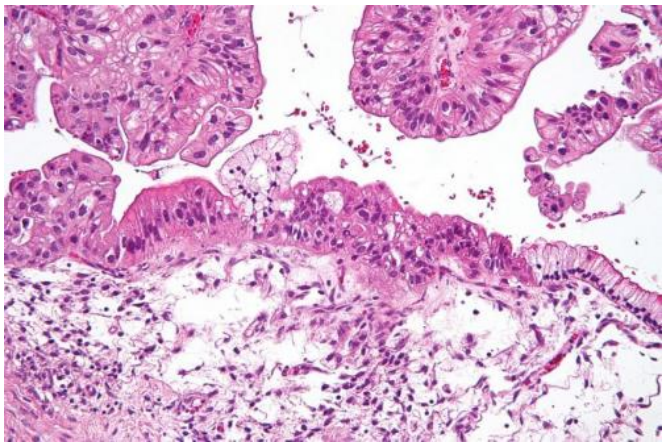

Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

A new study from a Massachusetts General Hospital (MGH) research team has found that the hypertension drug losartan, which targets the angiotensin signaling pathway, may improve the effectiveness of chemotherapy agents used to treat ovarian cancer. Previous research from the same team identified a similar effect for losartan in animal models of breast and pancreatic cancer, leading to a phase 2 clinical trial that had promising results against pancreatic cancer.

"We know that solid stress imposed by growing cancer cells and the extracellular matrix molecules they produce can compress blood vessels, reducing delivery of drugs and oxygen to tumors," says Lei Xu, Ph.D., of the Steele Laboratories for Tumor Biology in the MGH Department of Radiation Oncology, co-senior author of the report published online in *PNAS*. "The extracellular matrix itself can keep high-molecular-weight drugs from penetrating tumors, and angiotensin signaling contributes to matrix formation. Since levels of an important enzyme in the angiotensin pathway are elevated and associated with poor outcomes in ovarian cancer, we investigated whether use of losartan to decrease fibrosis could improve outcomes in animal models of ovarian cancer."

In a series of experiments in two mouse models the investigators found the following:

- Losartan treatment reduced extracellular matrix content and solid stress in ovarian tumors, increasing blood supply, oxygen levels and drug delivery;
- A mathematical model based on tumor physiology predicts that adding losartan to both low- and high-molecular-weight cancer therapies, delivered either intravenously or intraperitoneally, could improve outcomes;
- Adding losartan to treatment with the chemotherapy drug paclitaxel enhanced the antitumor effect of intraperitoneal paclitaxel and also reduced the development of ascites, accumulations of fluid in the abdomen that significantly reduce patients' quality of life;
- Losartan depleted the extracellular matrix by inducing the expression of antifibrotic miRNA molecules, which could be used as biomarkers for response or resistance to chemotherapy;

An analysis of records of patients who received standard treatment for ovarian cancer at MGH or Brigham and Women's Hospital while also also being treated for hypertension found that those patients taking losartan or other angiotensin-targeting drugs at the time of diagnosis lived an average of 30 months longer than did those taking other hypertension drugs.

"The entire class of angiotensin-targeting drugs that

includes losartan has been shown to reduce collagen accumulation in cardiac and renal fibrotic disease," says Xu, who is an assistant professor of Radiation Oncology at Harvard Medical School (HMS). "Losartan is a safe, and inexpensive drug that would cost less than $1/day while making a significant difference for patients with ovarian cancer."

Rakesh K. Jain, Ph.D., director of the Steele Labs, A.W. Cook Professor of Radiation Oncology at HMS and co-senior author of the *PNAS* report, adds, "Our findings—on top of the the beneficial results of the recent phase 2 trial for pancreatic cancer—should provide information and tools to explore a new therapeutic target for ovarian cancer, which leads to the death of around 14,000 women in the U.S. each year."

More information: Yanxia Zhao el al., "Losartan treatment enhances chemotherapy efficacy and reduces ascites in ovarian cancer models by normalizing the tumor stroma," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1818357116

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