Antiangiogenic treatment improves survival in animal model of ovarian cancer

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Epithelial ovarian cancer is the most lethal cancer of the female reproductive organs, with more than 200,000 new cases and more than 125,000 deaths each year worldwide. Because symptoms tend to be vague, 80 percent of these cancers are not recognized until the disease has advanced and spread to other parts of the body. The standard treatment for advanced ovarian cancer includes high-dose chemotherapy, which often results in debilitating side effects and for which the five-year survival rate is only 35 percent.

Now new research in an animal model finds that a novel combination therapy, which couples low-dose chemotherapy with an antiangiogenic treatment, resulted in better survival rates compared with standard therapy. Led by investigators at Beth Israel Deaconess Medical Center (BIDMC) and the University of Guelph, the findings show that the agent, 3TSR, not only led to tumor regression, but also improved tumor blood flow and enabled more efficient delivery of much smaller and less toxic doses of chemotherapy.

The study currently appears online in *The Journal of the Federation of American Societies for Experimental Biology (FASEB)* and will be published in the February 2015 print issue.

"The five-year survival rate for ovarian cancer has changed very little over the past 20 years and new treatment options are urgently needed, "says co-senior author Jack Lawler, PhD, an investigator in BIDMC's Center for Vascular Biology Research and Professor of Pathology at

Harvard Medical School. "High dose chemotherapy is usually required for the treatment of advanced ovarian cancer because the vascular supply to the tumor is inefficient and the cells inside the tumor have limited exposure to the chemotherapy drugs. Our results showed that when pretreated with an antiangiogenic agent, the animals responded to smaller, more frequent doses of chemotherapy, while still deriving more clinical benefit compared to current therapy protocols."

Like many other types of cancer, ovarian cancer obtains nutrients and oxygen by inducing the growth of new blood vessels, a process known as angiogenesis. Antiangiogenic approaches to treat cancers attempt to disrupt the balance between promoters and inhibitors of angiogenesis, either by inhibiting proangiogenic factors or by increasing antiangiogenic molecules.

The Lawler laboratory at BIDMC investigates thrombospondin-1 (TSP-1), the first naturally occurring protein to be identified as an angiogenesis inhibitor. "What we're trying to do is to boost the antiangiogenic side of the balance in order to deprive the tumor of blood supply and halt growth," he says.

Previous work by Lawler and others had revealed that a portion of TSP-1 known as 3TSR interacts with another protein, CD36, which is found on the surface of endothelial cells that line the blood vessels. Together, the two molecules cause endothelial cells to stop growing and die, reducing blood vessel growth and disrupting the tumor's ability to survive. The new findings revealed that 3TSR was acting on more than just endothelial cells and was directly inhibiting growth of ovarian tumor cells. "We think this might be occurring because, like endothelial cells, ovarian cancer cells contain CD36," says Lawler. "The sensitivity of the tumor cells to 3TSR means that both endothelial and tumor cells can be targeted with a single reagent."

Many of the blood vessels in tumors don't function properly to distribute blood because they are not correctly formed; these blood vessels are destroyed during the early phase of antiangiogenic treatment, resulting in a period of time when blood flow to the tumor improves. In this new paper, Lawler, and co-senior author Jim Petrik, PhD, of the University of Guelph, wanted to find out if 3TSR would enhance uptake of chemotherapy drugs delivered through lower-dose "metronomic" regimen.

They conducted a series of experiments in which mouse ovarian cancer cells were injected into an animal model and allowed to grow until they exhibited features similar to patients with advanced disease, namely the spread of small tumors throughout the abdomen and the accumulation of fluid called ascites.

"This is the advanced stage at which most women are first diagnosed with ovarian cancer," explains Lawler. The investigators then treated the mice with either intermittent doses of standard high-dose chemotherapy or with more frequent doses of low-dose chemotherapy. In each case, the chemotherapy was either administered on its own or in combination with pretreatment with 3TSR.

The end result for the pretreated mice receiving the smaller chemotherapy doses was a smaller tumor, with improved blood supply. "We were able to exploit this enhanced blood supply to improve chemotherapy drug delivery to the tumor, with excellent clinical effect," adds Lawler. "The benefit of this approach is that we can create an environment that increases the efficiency of drug delivery, enabling the use of significantly lower doses of the chemotherapeutic agents and thereby reducing the side effects associated with the treatment."

"The clinical implications are significant," he adds. "With this approach, patients could receive significantly smaller doses of chemotherapy drug

while deriving greater clinical benefit, compared to current therapy protocols. We hope that this will soon be tested in clinical trials."

Provided by Beth Israel Deaconess Medical Center