Researchers detail possible resistance mechanisms of colorectal cancer to bevacizumab (Avastin)

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A University of Colorado Cancer Center study published in the journal *PLOS ONE* shows that when colorectal cancer is targeted by the drug bevacizumab (Avastin), tumors may switch dependence from VEGF-A, which is targeted by the drug, to related growth factors in including VEGF-C, VEGF-D and placental growth factor. This change to new growth-factor dependence may allow colorectal cancer to push past bevacizumab's blockage of VEGF-A to continue to drive tumor growth.

"Think of it like damming a river. Bevacizumab can block the main flow, but then once a tumor's need builds up behind this dam, water starts to flow around the blockage in the form of streams and tributaries. That's like these other growth factors – eventually a tumor becomes able to use these tributaries of VEGF-C, VEGF-D and placental growth factor to supply itself with the 'water' it needs," says Christopher Lieu, MD, investigator at the CU Cancer Center and assistant professor of Medical Oncology at the University of Colorado School of Medicine.

The analogy of liquid is an apt one – bevacizumab slows cancer's growth by limiting a tumor's ability to grow the new blood vessels it needs to supply itself with nutrients. Especially in combination with chemotherapy, bevacizumab has proved an effective treatment for colorectal cancer. But then there frequently comes a point at which bevacizumab stops working and the tumor restarts its growth. This study asked why.

Specifically, Lieu and colleagues serially tested the levels of other VEGF-related growth factors in 42 patients treated with bevacizumab and chemotherapy, at many points during the course of their treatment.

"What we saw is that levels of VEGF-C and placental growth factor went up just before tumors progressed and then stayed high during the periods of tumor growth. Interestingly, VEGF-D was only elevated during progression. But it seems that tumors may be using these growth factors as ways to create blood vessel growth in the absence of VEGF-A, blocked by bevacizumab," Lieu says.

Then the researchers also took a snapshot of levels in 403 colorectal cancer patients, at one time during treatment. Because this group included patients who were and were not being treated with chemotherapy along with bevacizumab, they could show that the rise in VEGF levels was, in fact, due to bevacizumab and not to some interaction with the chemotherapy.

"It's too early to say with certainty that VEGF-C, VEGF-D, and placental growth factor are the cause of colorectal cancer resistance to bevacizumab, but the correlation we saw in this study is compelling," Lieu says.

Current studies are exploring the use of drugs that block more blood-vessel-growth-promoting factors than VEGF-A. For example, Lieu points to the example of aflibercept (Zaltrap), which was given FDA approval in August, 2013 for the treatment of metastatic colorectal cancer, along with the chemotherapy regimen known as FOLFIRI. The drug inhibits placental growth factor along with VEGF-A.

"It's an attractive strategy, and also proof of concept that by targeting not only the primary mechanism of tumor growth but also one or more of these 'workarounds,' this drug or other future drugs could stall growth

longer than blocking any one of these growth factors, individually," Lieu says.

Lieu points out that in addition to targeting these additional growth factors, the fact that spikes in VEGF-C and placental growth factor presage tumor progression could give doctors and researchers a clue that bevacizumab has lost its efficacy. Though more work is needed, Lieu can imagine using spikes in VEGF-C or prenatal growth factor to recommend evaluating new treatment options.

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