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Researchers identify genetic variants linked to toxic side effects from bevacizumab

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In the largest study of its kind, researchers have found two common genetic variants that can be used to predict whether or not cancer patients might suffer severe adverse side-effects from the drug bevacizumab.

The study is unique because researchers found and analysed hundreds of thousands of genetic variations in all the genes of more than 1,000 patients with advanced breast, prostate or pancreatic cancer taking part in five clinical trials in the U.S.. This genome-wide association study (GWAS) is the largest such study in patients being treated with bevacizumab and it is to be presented at the 32th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, which is taking place online.

Bevacizumab is a monoclonal antibody that targets a protein called vascular endothelial growth factor (VEGF) that helps cancer cells grow new blood supplies. By targeting VEGF, the drug reduces the supply of oxygen and nutrients so that the tumour shrinks or stops growing. It is used to treat a number of different cancers, often in combination with other drugs.

Federico Innocenti, associate professor at the Eshelman School of Pharmacy of the University of North Carolina in Chapel Hill, U.S., who led the research, said: "VEGF inhibitors like bevacizumab have revolutionised cancer treatment, but because they work by impacting how the body builds and regulates blood vessels, side effects are usually

vascular-related. Patients treated with bevacizumab can experience an increase in blood pressure and kidney problems caused by proteins leaking into urine. These toxicities are common, and have been observed in up to 40% of patients treated with bevacizumab. They can cause discomfort and harm to patients; they can develop quickly and become severe, even fatal; and they can lead to delaying or discontinuing treatment, which limits their efficacy.

"Currently, there is no way of identifying patients who are likely to experience these toxicities. Some of this risk is likely to be due to each individual patient's genetic make up, and so we set out to identify new genes and their variants that may improve the prediction and management of bevacizumab-induced adverse side effects.

"We characterised hundreds of thousands of genetic variations in more than 1,000 patients. We were not looking for variations in the tumour DNA, but rather the heritable DNA of the patients—the same DNA that determines inherited characteristics like eye colour, height and many others. A group of these patients experienced the side effects of high blood pressure and kidney toxicity, and so we compared the frequency of DNA variations between these patients and the patients who did not suffer these side effects. In this way we were able to discover a series of variations that increased or reduced the risk of these toxicities."

The researchers identified ten variations (known as SNPs) associated with high blood pressure and ten with kidney toxicity. Then, because it is important to test if the variation produces the same effect in as many other studies as possible, they investigated two variations linked to high blood pressure in a different group of 582 patients. One of these variations, called rs6770663, which is located in the KCNAB1 gene, was significantly associated with an increased risk of systolic blood pressure of 160mm Hg or more.

"This finding is important, providing further evidence for the possible use of this variant as an indicator of the risk of toxicity from bevacizumab. It appears twice as often in patients experiencing high blood pressure as in those who do not," said Prof Innocenti. "In addition, KCNAB1 generates instruction for the production of a protein that regulates the function of potassium channels in blood plasma membranes. Reduced function of this protein increases blood vessel constriction, and we think that patients with rs6770663 have greater narrowing of the blood vessels in response to bevacizumab treatment, resulting in an increased risk of high blood pressure. The biological basis for this finding is quite strong."

For protein leaking into the urine (proteinuria) and causing kidney problems, the most significant variation was rs339947, located between the DNAH5 and TRIO genes. TRIO induces activity of a protein that contributes to damage in the kidney, which can lead to proteinuria. This has not yet been tested in another group of bevacizumab-treated patients and so requires further validation.

The findings will enable doctors to improve the treatment of their patients and avoid severe adverse side effects, for instance, by treating those with the rs6770663 variant with another drug, if available, by giving a reduced dose of bevacizumab to see what happens, by increased monitoring, or by giving bevacizumab with other drugs that stop blood pressure rising.

"rs6770663 can be regarded as a new, validated biological marker to predict high blood pressure caused by bevacizumab. Before treatment with bevacizumab, this variant can be searched for in the DNA of patients with a simple genetic test. If it is found, physicians can decide about various treatment options," said Prof Innocenti. "Early identification is a potential double win—it will help doctors identify who is at risk and apply different interventions. The rs6770663 variation is

found in up to 20% of people of European origin, 30% of Asian origin, and 80% of people of African origin, so these findings can have an impact on a considerable number of people."

The researchers are continuing to validate rs6770663 and the other variants in different groups of patients, including those of different ethnicities. They are also investigating whether these variants can predict high blood pressure and kidney toxicity for other anti-cancer drugs.

"Efforts are now underway to set up a prospective observational study that will give doctors and patients a test to screen patients and update their treatment regimens as necessary. Interested clinicians and scientists should contact me," concluded Prof Innocenti.

William R. Sellers, Professor of Medicine at the Dana-Farber Cancer Institute, Harvard Medical School, U.S., is co-chair of the EORTC-NCI-AACR Symposium on behalf of the NCI and was not involved with the research. He commented: "This study is a good example of how our increasing ability to study the human genome easily and in depth is producing findings that may have an impact, either immediately or fairly soon, on patient health and outcomes. Side effects from bevacizumab can be extremely debilitating, so if we can use a simple genetic test to identify which patients will experience toxicities and take appropriate measures to avoid these toxicities, this could help to provide better and more effective treatments for our patients."

More information: Abstract no: 6, "Bevacizumab-induced hypertension and proteinuria: A genome-wide analysis of more than 1,000 patients", by Federico Innocenti et al., presented in the Late-breaking proffered papers session, 15.45-17.15 hrs CEST, Sunday 25 October, channel 1: cm.eortc.org/cmPortal/Searchab … ctdetails/0000897110

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