

Imaging studies may predict tumor response to anti-angiogenic drugs

November 4 2013

Advanced imaging techniques may be able to distinguish which patients' tumors will respond to treatment with anti-angiogenic drugs and which will not. In patients newly diagnosed with the dangerous brain tumor glioblastoma, Massachusetts General Hospital (MGH) researchers report, those for whom treatment with the anti-angiogenic drug cediranib rapidly 'normalized' abnormal blood vessels around their tumors and increased blood flow within tumors survived significantly longer than did patients in whom cediranib did not increase blood flow. The report appears in *PNAS Early Edition*.

"Two recent phase III trials of another anti-angiogenic drug, bevacizumab, showed no improvement in overall survival for [glioblastoma](#) patients, but our study suggests that only a subset of such patients will really benefit from these drugs," explains Tracy Batchelor, MD, director of the Pappas Center for Neuro-Oncology at the MGH Cancer Center and co-lead and corresponding author of the current study. "Our results also verify that normalization of [tumor](#) vasculature appears to be the way that anti-angiogenic drugs enhance the activity of chemotherapy and [radiation](#) treatment."

Anti-angiogenic drugs, which block the action of factors that stimulate the growth of blood vessels, were first introduced for cancer treatment under the theory that they would act by 'starving' tumors of their blood supply. Since that time, however, new evidence has suggested that the drugs' benefits come through their ability to 'normalize' the abnormal, leaky vessels that usually surround and penetrate tumors, improving

delivery of both [chemotherapy drugs](#) and the oxygen that is required for effective radiation therapy. This hypothesis was first proposed and has subsequently been developed by Rakesh Jain, PhD, senior author of the current study and director of the Steele Laboratory for Tumor Biology in the MGH Department of Radiation Oncology.

A 2007 clinical study led by Batchelor found evidence suggesting that cediranib, which has not yet received FDA approval, could temporarily normalize tumor vasculature in recurrent glioblastoma, but it was not clear what role normalization might have in patients' survival. In the past few years, several research teams with leadership from Batchelor, Jain and other co-authors of the current paper reported evidence that cediranib alone improved blood perfusion within recurrent glioblastoma tumors in a subset of patients and improved their survival. A *Nature Medicine* study published earlier this year used a technique called vessel architectural imaging (VAI), developed at the Martinos Center for Biomedical Imaging at MGH, to reveal that cediranib on its own improved the delivery of oxygen within tumors of some patients with [recurrent glioblastoma](#).

Patients in the current study were participants in a clinical trial of cediranib plus radiation and chemotherapy for postsurgical treatment of newly diagnosed glioblastoma. Among participants in that trial, 40 also had advanced brain imaging with VAI and other MR imaging techniques. While all but one of the participants in the overall trial showed some evidence of vascular normalization and reduced edema – tissue swelling that can be dangerous within the brain – of the 40 who had imaging studies, only 20 were found to have persistent improvement in vessel perfusion. VAI also revealed improved oxygen delivery only in the patients with improved perfusion. Those patients ended up surviving about 9 months longer – 26 months, compared with 17 months – than did those whose perfusion levels remained stable or worsened. A comparison group of glioblastoma patients treated with radiation and

chemotherapy only survived an average of 14 months.

"It's quite likely that the results we've found with cediranib will apply to other anti-angiogenics," Batchelor says. "In fact a presentation at a recent meeting showed that patients with improved perfusion from bevacizumab were also the ones in that study who lived longer. More research is needed, but these findings suggest that MR imaging techniques should play an essential role in future studies of anti-angiogenic drugs in glioblastoma and possibly other types of solid tumors. We've received National Cancer Institute funding to study this approach with bevacizumab treatment, and we will also be investigating tumor delivery of chemotherapy and oxygen status using combined MR/PET techniques at the Martinos Center's MR/PET facility."

Jain adds, "We originally introduced the normalization hypothesis for anti-angiogenic [treatment](#) in 2001, but it's taken more than a decade to confirm that vascular normalization actually increases tumor perfusion and that increased perfusion, rather than tumor starvation, is what improves survival. This study provides compelling evidence that normalization-induced increased vessel [perfusion](#) is the mechanism of benefit in glioblastoma [patients](#)." Jain is the Cook Professor of Radiation Oncology (Tumor Biology), and Batchelor is the Armenise-Harvard Professor of Neurology at Harvard Medical School.

More information: Improved tumor oxygenation and survival in glioblastoma patients who show increased blood perfusion after cediranib and chemoradiation,

www.pnas.org/cgi/doi/10.1073/pnas.1318022110

Provided by Massachusetts General Hospital

Citation: Imaging studies may predict tumor response to anti-angiogenic drugs (2013, November 4) retrieved 19 July 2023 from

<https://medicalxpress.com/news/2013-11-imaging-tumor-response-anti-angiogenic-drugs.html>

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