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Value of correlative biomarkers in understanding tumor biology

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We appreciate the insightful review of our article Batchelor *et al*. "Improved tumor oxygenation and survival in glioblastoma patients who show increased blood perfusion after cediranib and chemoradiation" by Dr. Burt Nabors (1,2). In his commentary, he skillfully highlights the initial enthusiasm followed by more measured interest for anti-angiogenic agents in glioblastoma (GBM) (1). Based on the robust angiogenesis that characterizes GBM, there exists a strong biological rationale for targeting tumor blood vessels and, fundamentally, blood flow and nutrient delivery are essential to tumor survival. The therapeutic challenge with this class of agents has been identifying those patients likely to benefit and achieve a durable response both clinically and radiographically.

In our study of newly diagnosed GBM patients treated with radiation, temozolomide, and cediranib, an oral VEGFR inhibitor, we incorporated both blood and imaging markers to track changes in vascular structure and function. The goal was to better understand the physiological impact of anti-angiogenic therapy. As Dr. Nabors pointed out, we found that those patients with increased perfusion to the tumor had improved tissue oxygenation and lived longer-likely because of better delivery of temozolomide and oxygen (necessary for radiation efficacy) to the tumor resulting in improved tumor cell kill. Furthermore, we identified that blood biomarkers, specifically PlGF and sVEGFR2, were useful pharmacodynamic biomarkers of response whereas Il-8 and sVEGFR1 were biomarkers of relapse.

Critically, the imaging and blood biomarkers we explored are noninvasive and can be performed serially to track changes in the tumor over time. A particular challenge with brain tumors is the limited access to serial tissue biopsies to shed light on how the tumor and its microenvironment evolves in response to therapeutic pressures. Having a tool such as MRI where signal changes reflect physical processes in the brain is essential to interpret responses and help guide therapeutic decisions or potential combination therapies (3). MRI also has the benefit of capturing known tumor heterogeneity since the entire volume of an individual tumor is visualized as well as separate tumors in the same patient. Consequently, a crucial step to improving the care of brain tumor patients is to optimize correlative biomarkers that shed light on biological changes and use the human as the experimental model so we can learn as much as possible about the effects of drugs being developed for this challenging disease. The more we learn from our patients, the better we can design the next wave of therapies (4).

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