MEDICAL ONCOLOGY

Vascular normalization predicts response to cediranib

Several predictive biomarkers have been proposed for anti-VEGF therapies; however, no validated biomarkers for cancer treatment exist. For patients with glioblastoma, who have a dismal prognosis, early imaging biomarkers or blood biomarkers of response to therapy are urgently needed to enable tailored antiangiogenic therapy. Glioblastomas secrete high levels of VEGF, which cause increased vascular permeability and vasogenic edema. Blockade of VEGF signaling with anti-VEGF agents can reverse these effects but can also result in difficulties in assessing tumor response by MRI. Sorensen *et al.* used an advanced MRI technique that enabled them to show that evaluation of biomarkers 1 day after treatment with the anti-VEGF agent, cediranib, can predict progression-free survival and overall survival in patients with recurrent glioblastoma.

Preclinical and clinical data have suggested that vascular normalization by cediranib might benefit glioblastoma patients, and phase II data in 16 patients with recurrent glioblastoma showed cediranib decreased vessel diameter and permeability 1 day after treatment. In the phase II study, transient increases in plasma IV collagen levels correlated with reductions in edema, as a result of transient vascular normalization. The researchers, therefore, hypothesized that changes in three biomarkers (vascular permeability and flow, microvessel volume

and circulating collagen IV levels) related to vascular normalization 1 day after treatment would predict improved survival in patients with recurrent glioblastoma.

Sorensen *et al.* used dynamic contrast-enhanced MRI to measure treatment response to cediranib and vascular parameters in 31 patients with recurrent glioblastoma. Several of the assessed parameters related to vascular normalization changed after 1 day of cediranib treatment. Changes in microvessel cerebral blood volume (CBV), permeability (as measured by K^{trans}) and plasma collagen IV levels correlated with survival outcomes. A greater reduction in K^{trans} was observed after a single dose of cediranib in patients with increased progression-free survival and overall survival compared to those without such a benefit. Moreover, an increase in tumor microvessel CBV after one dose of cediranib was observed in patients with prolonged overall survival. Likewise, increases in plasma collagen IV levels were seen in patients with extended progression-free survival. These three parameters were combined into a composite vascular normalization index to determine whether their measurement could accurately predict outcomes of cediranib therapy. Index scores correlated closely with increased progression-free survival and overall survival outcomes.

The vascular normalization index differentiated patients with favorable

A. Gregory Sorensen, A. Martins Center for Biomedical Imaging, Boston, MA, USA

versus unfavorable outcomes after a single cediranib dose. The researchers suggest that evaluating the degree of tumor vascular normalization immediately after anti-VEGF treatment could potentially be used to predict improved outcomes for patients with glioblastoma. The results of this study indicate that the ability to detect changes in tumor parameters after only 1 day of treatment may permit tailoring of treatment to the patients most likely to benefit from it, while enabling therapy to be discontinued in those who will not respond. The authors plan to validate the vascular normalization index as a predictive biomarker in larger, prospective studies in patients with recurrent glioblastoma.

Lisa Hutchinson

Original article Sorensen, A. G. *et al.* A "vascular normalization index" as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients. *Cancer Res.* **69**, 5296–5300 (2009).