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Maximizing the Efficacy of Angiogenesis Inhibitors

TO THE EDITOR: The article "Phase II Study of Aflibercept in Recurrent Malignant Glioma: A North American Brain Tumor Consortium Study" by de Groot et al[1] was published in *Journal of Clinical Oncology*. We commend the authors for investigating correlations between gene expression and clinical outcome and believe that their findings may provide important clues for maximizing the efficacy of antiangiogenic therapies.

de Groot et al[1] find that hypoxia-related markers, including hypoxia-inducible factor 1α (*HIF-1*α) expression, are correlated with longer time to progression (TTP) after aflibercept treatment. On the other hand, they find that other markers including *CXCR4* are correlated with shorter TTP. These results are striking, because *HIF-1*α is known to promote expression of *CXCR4*.[2] Why then would these two genes have opposite associations with TTP?

One possible explanation is the presence of a positive feedback loop. Although *HIF-1*α induces expression of *CXCR4*, CXCR4 signaling is known to activate the Jak2/signal transducer and activator of transcription 3 (STAT3) signaling pathway,[3] and STAT3 signaling is known to trigger expression of both *HIF-1*α and vascular endothelial growth factor (*VEGF*).[4] Simply put, suppression of VEGF may be ineffective if CXCR4 levels are high enough to rapidly induce additional VEGF at the tumor site.

As a first step toward exploring this hypothesis, de Groot et al[1] could use their existing data to further explore relationships between *CXCR4* expression, *HIF-1*α expression, and TTP in individual patients. The authors might also consider examining expression of other genes regulated by STAT3. Regardless of whether these factors are predictive or prognostic, understanding the relationship between them will provide important biologic insights. Several studies have already identified STAT3 as an important factor in glioma[5,6]; *CXCR4* is known to be highly expressed on glioma cells,[7,8] and *HIF-1*α expression increases with glioma progression.[9] The presence of a feedback loop would help connect these three disparate sets of observations.

The same feedback loop may also function in other cancers, especially because *CXCR4* expression is prognostic in colorectal cancer.[10] The need for predictors of response to antiangiogenic therapies in breast cancer is well established,[11] and a CXCR4–Jak2/STAT3–HIF-1α feedback loop could provide another avenue to address this need.

If a feedback loop is indeed at work in patients with less favorable responses, then combining an angiogenesis inhibitor with a CXCR4 antagonist (such as AMD3100) and/or an inhibitor of Jak2/STAT3 signaling (such as AZD1480 or CEP-701) may help those patients achieve better outcomes. One such trial is already planned,[12] and it is certainly worthwhile to assay expression of *HIF-1*α and *CXCR4* in such studies.

In summary, de Groot et al[1] report the counterintuitive finding that *HIF-1*α and *CXCR4* are respectively associated with longer and shorter TTP in patients treated with aflibercept. One possible explanation for this is the presence of a positive feedback loop involving STAT3. If further investigation supports this hypothesis, it would suggest that combining a CXCR4 antagonist and/or Jak2/STAT3 inhibitor with an angiogenesis inhibitor could help more patients with cancer gain the full benefit of this innovative class of medicines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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