Can the Lung Cancer Pie Be Divided into Angiogenic Slices?

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Running Title: Predictive Markers for VEGF and EGFR Inhibition in NSCLC

Disclosure of Potential Conflicts of Interest

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Summary

There are no validated markers for predicting benefit from angiogenesis inhibitors or classifying tumors with distinct angiogenic phenotypes. In NSCLC patients treated with bevacizumab and erlotinib, Franzini and colleagues find that angiogenesis- and hypoxia-associated gene expression signatures predict tumor response and/or clinical outcome, and may define distinct angiogenic patterns.
In this issue of Clinical Cancer Research, Franzini and colleagues (1) investigate the association between angiogenesis- and hypoxia-related gene expression signatures and clinical outcome in non-squamous non-small cell lung cancer (NSCLC) patients treated with the Vascular Endothelial Growth Factor (VEGF) inhibitor bevacizumab plus the Epidermal Growth Factor Receptor (EGFR) inhibitor erlotinib. A remarkable advance in the treatment of NSCLC, and other cancers, is the development of biomarker-defined classifications that help define subgroups likely to benefit from particular targeted agents. The major genomically-defined “slices of the pie” for NSCLC are now familiar, such as those marked by EGFR, ALK, or BRAF alterations. Immunotherapy is rapidly moving in a similar direction; emerging data already supports that tumors expressing varying amounts of PD-L1 on tumor or immune cells may derive different degrees of benefit from agents targeting the PD-1/PD-L1 axis, and more refined immune classifications are no doubt on the way (2).

Given this progress, it is perhaps surprising that after about two decades of testing angiogenesis inhibitors such as the anti-VEGF monoclonal antibody bevacizumab, we still do not have clinically useful markers for classifying tumors based on their angiogenic phenotype, or for predicting which patients are more likely to benefit from these drugs. This is surely an important unmet need, given that only a minority of patients derive significant benefit from bevacizumab, serious toxicities may occur, and resistance inevitably occurs.

Bevacizumab significantly improves clinical outcomes when added to platinum-based chemotherapy in NSCLC (3). The addition of bevacizumab to erlotinib did not prolong survival compared with erlotinib in the overall platinum-refractory NSCLC
population, but two randomized phase III studies suggest that bevacizumab plus erlotinib may be superior to erlotinib alone among EGFR mutation positive patients (4, 5). Outside of EGFR mutation, there are currently no validated markers for identifying which patients are more likely to benefit from bevacizumab when added to either chemotherapy or erlotinib.

Franzini and colleagues (1) performed gene expression profiling on bronchoscopic biopsies from 42 patients with stage IIIB/IV non-squamous NSCLC enrolled in the Swiss Group for Clinical Cancer Research 19/05 phase II trial (6) and treated with bevacizumab and erlotinib. Pretreatment gene expression profiles were correlated with clinical outcomes (tumor shrinkage [TS], time to progression [TTP], and OS) and then subjected to gene set enrichment analysis (GSEA) using a 43-gene core angiogenesis signature and a 51-gene hypoxia signature, previously reported. GSEA revealed that both angiogenic and hypoxic-associated signatures are enriched within genes that associate with TTP under bevacizumab and erlotinib therapy. Further unsupervised hierarchical clustering of the top 10-ranked angiogenesis-associated genes revealed that patients with increased expression of angiogenic genes at baseline (low risk) possess an improved median TTP (7.1 months) versus a 2.1 month median TTP in patients with a decreased signature (high risk). Patients with a diminished hypoxia-signature (low-risk) had a prolonged median TTP (6.9 months) versus a 2.9 month median TTP in patients with elevated levels (high risk).

Unlike the angiogenesis signature, increased expression of the hypoxia signature was predictive of TS after 12 weeks of bevacizumab plus erlotinib, suggesting that it may possess greater potential for assessing treatment response. Furthermore, both signatures...
were found to have prognostic value for OS, as the median OS for patients with elevated hypoxia signature expression was 9.9 months versus 17.8 months in patients with decreased levels. While hypoxia-inducible factor 1-alpha (HIF-1α) was not identified as predictive for TTP, several of its downstream targets were components of the hypoxia signature. These results agree with previously reported studies demonstrating that hypoxia correlates with a more aggressive phenotype, perhaps by enhancing malignant potential through increased genomic instability and by acting as selective pressure for variants with diminished apoptotic potential (7).

Assuming the associations described between the angiogenic and hypoxia response signatures are robust, important issues would need to be addressed before they could be used in selecting therapy. In the absence of a control arm, it is not possible to determine whether the signatures are predictive of benefit for bevacizumab plus erlotinib compared with another therapy, or merely prognostic. Caution should be used in assuming that markers associated with improved clinical outcome in a single arm study will be predictive of greater relative benefit compared with another drug in a randomized study. For example, we previously observed that high circulating IL-6 is a negative prognostic marker in metastatic renal cell cancer, but predicts greater relative benefit for patients receiving pazopanib compared with placebo control (8). Such observations would not be evident in a single arm study.

Clinically useful predictive biomarkers typically help inform the choice between different therapies. It remains to be seen whether the angiogenic or hypoxia signatures could be used to predict, for example, which patients benefit from bevacizumab in combination with chemotherapy compared with chemotherapy alone. Interestingly, the
authors report an association between the hypoxia signature and PFS in the sorafenib, but not erlotinib, arm of the BATTLE study, suggesting the signature may have utility for other drugs targeting the VEGF pathway (9, 10).

Given the current NSCLC landscape, it would also be important to assess whether the signatures are predictive of benefit within the standard molecularly defined subgroups. As noted above, bevacizumab appears to add greater benefit in the EGFR mutation positive subgroup (4, 5). It would therefore be important to assess the signatures in the EGFR-mutant and wild-type groups separately. The mechanism underlying the apparently increased sensitivity of EGFR mutant tumors to VEGF blockade is not well understood, but it is noteworthy that constitutive EGFR pathway activation results in upregulation of VEGF and the HIF-1α pathway (11), suggesting there may be overlap between EGFR and VEGF pathway dependence.

The authors suggest that the signatures are associated with distinct vascular patterns; for example, vessels from tumors most likely to respond to bevacizumab and erlotinib appear to possess a greater level of integrity and are less permeable compared with vessels supplying less responsive tumors. It is known that expression levels of genes encoding proteins critical to endothelial barrier function and vessel integrity are elevated in tumors of patients with improved response to bevacizumab and erlotinib. The authors conclude that when angiogenesis-associated genes are diminished, tumor angiogenesis is dysregulated, resulting in hyperpermeable vasculature, increased hypoxia and earlier disease progression (Fig. 1). Previous studies illustrate that different angiogenic phenotypes impact tumor response to angiogenesis inhibition. For example, we previously showed (12) that NSCLC xenografts which were less responsive to prolonged...
bevacizumab are supplied by tortuous and pericyte-devoid tumor-associated vessels, whereas a more normalized revascularization characterizes NSCLC xenografts with acquired resistance to long-term treatment.

It is now widely accepted that genomic phenotypes of a variety of cancers, such as EGFR mutant NSCLC or BRAF mutant melanoma, impact the response to targeted therapeutic strategies in distinct subgroups of patients. However, the search for biomarkers capable of defining distinct angiogenic phenotypes, and identifying NSCLC patients most likely to derive clinical benefit from anti-angiogenic therapies, has proved challenging. The findings reported by Franzini and colleagues (1), while not ready for immediate clinical application, may be a promising step forward towards addressing our collective hunger for angiogenic slices of the NSCLC pie.

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References


**Figure 1.** Angiogenesis- and hypoxia-associated gene expression signatures predict response of NSCLC tumors to combined bevacizumab and erlotinib therapy. Patients with tumors characterized by a robust angiogenesis gene signature and a decreased hypoxia-associated gene signature (upper panel) display increased tumor shrinkage and improved outcome. Gene expression data predict that tumor-associated vascular bed of these tumors is formed through controlled, sustained angiogenesis and that the vasculature is less permeable compared with the vascular network supplying highly hypoxic tumors, which are less responsive to therapy (lower panel). Abbreviations: OS, overall survival; pO2: partial pressure of oxygen; TS, tumor shrinkage; TTP, time to tumor progression; VEGF, vascular endothelial growth factor.
Figure 1:

- **Tumor cell**
- **Pericyte**
- **Endothelial cell**
- **Macromolecule**
- **VEGF**
- **Bevacizumab**
- **Erlotinib**

- **pO2**

↑ TS
↑ TTP
↑ OS

↓ TS
↓ TTP
↓ OS

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