Multiple Cytokine and Growth Factor Serum Biomarkers Predict Therapeutic Response and Survival in Advanced-Stage Head and Neck Cancer Patients

□□*Commentary on Allen et al., p. 3182*

William L. Bigbee,[1,2] Jennifer R. Grandis,[1] and Jill M. Siegfried[2]

In this issue of *Clinical Cancer Research*, Allen et al. (1) report that serum levels and temporal velocities of multiple cytokine and growth factors interleukin IL-6, IL-8, growth regulated oncogene 1 (GRO-1), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF), secreted by tumor and stromal cells and modulated by transcription factor nuclear factor κB (NF-κB), predict chemoradiation response and survival in patients with advanced-stage oropharyngeal carcinoma. This article reports important and significant translational results from the largest study to date in head and neck squamous cell carcinoma (HNSCC) patients of the relationship between baseline levels and longitudinal changes in these individual serum cytokine levels and multiplexed NF-κB–related panels with cause-specific and disease-free survival. These findings have potential clinical significance due to the fact that conventional tumor-node-metastasis staging does not accurately predict survival in many patients.

The generalized biological basis and scientific rationale of this study rest on known tumor/host cell biology showing that the interaction of tumor and stromal cells leads to the secretion of multiple growth factors and cytokines that modulate and promote cell growth, inflammation, and angiogenesis within the tumor microenvironment (2–4) and hence is related to tumor proliferation, invasion, and metastasis (5, 6). The current study builds on previously reported data from these and other investigators that increased expression of a number of cytokines and growth factors is observed in HNSCC cell lines and tumor tissues (7–15). Of specific relevance, these investigators have previously observed increased levels of factors IL-6, IL-8, GRO-1, VEGF, and HGF in the sera of HNSCC patients compared with disease-free control subjects (9, 12, 16–20), consistent with previous and related studies (9, 21–24). These observations, together with their finding that the levels of several of these factors can be jointly modulated in HNSCC by the transcription factor NF-κB, led these investigators to hypothesize that the circulating levels of these factors could be combined into a biologically rational biomarker panel for more accurately predicting response, relapse, and survival in individual patients. In addition, building on previous observations that increases or decreases in the levels of IL-6, IL-8, GRO-1, VEGF, and HGF in post-chemoradiation serum samples were associated with tumor progression or reduction in individual patients, these investigators further reasoned that longitudinal monitoring of a panel of these NF-κB–modulated proteins could potentially serve as additional serum biomarker predictors of response, relapse, and survival.

To test these hypotheses, the investigators used the standardized multiplexed immunoassay Luminex platform using addressable beads and flow cytometry (25, 26)[3] to obtain quantitative measurements of these analytes in serum samples collected at baseline and every 3 months (3, 6, 9, and 12 months posttreatment) from 30 patients with a pathologic diagnosis of stage III or IV oropharyngeal carcinoma and treatment with combined chemoradiation but not surgery. This longitudinal monitoring of the serum biomarker panel revealed that the overall directional change in these serum analyte levels was associated with early tumor response and, in patients with the largest rate of change of these combined five biomarkers, poorer cause-specific survival. Formal Kaplan-Meier survival analysis showed that individual patients with the largest positive slopes for three or more of these analytes had significantly worse disease-free survival. Interestingly, including smoking history in the multivariate analysis model revealed that patients with a history of smoking also tended to have greater analyte slopes and decreased survival, consistent with the prior observation of the inducible activation of NF-κB–related cytokines by tobacco smoke exposure. Importantly, after adjustment for smoking history, large longitudinal increases in three of the related serum factors, IL-6, VEGF, and HGF, independently conferred 3.8-, 3.0-, and 2.9-fold relative risk of death, respectively, and in individual patients, large increases in the upper quartile of any three or more analytes predicted poorer cause-specific survival.

In summary, and as noted by the investigators, this article reports important and significant translational results from the largest study to date in HNSCC patients of the relationship between baseline levels and longitudinal changes in individual serum cytokine levels and multiplexed NF-κB–related panels with cause-specific and disease-free survival. The scientific rationale and experimental approach undertaken in this study are innovative including the emerging paradigm of using multiple markers for association with clinical variables and patient outcomes as well as the use of multiple measurements

Authors' Affiliations: [1]Head and Neck Cancer Program, [2]Lung and Thoracic Malignancies Program, University of Pittsburgh Cancer Institute, The Hillman Cancer Center, Pittsburgh, Pennsylvania

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Requests for reprints: William L. Bigbee, University of Pittsburgh Cancer Institute, The Hillman Cancer Center, UPCI Research Pavilion Suite 2.26d, 5117 Centre Avenue, Pittsburgh, PA 15213-1863. Phone: 412-623-3231; Fax: 412-623-7768; E-mail: bigbeewl@upmc.edu.

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[3] http://www.luminexcorp.com

over time in patients to determine the additional value of rate-of-change biomarker data in addition to point-in-time quantitative levels. The study's overall finding that increases in individual or multiple serum analytes are significantly associated with patient outcome during the first year following treatment shows that longitudinal monitoring of these NF-κB–related analyte panels may provide important complementary prognostic information to existing clinical monitoring and imaging during a time period when surgical intervention and/or adjuvant therapy is an option in HNSCC patients with a poor predicted outcome. These important results extend the previously reported observations of Hathaway et al. (27) that multiplexed quantitative analysis of panels of serum analytes associated with the pathogenesis and progression of HNSCC can provide clinically useful metrics for monitoring individual patient responses to therapy and lead time of treatment failure ultimately leading to improved patient outcomes.

The coordinate increase in the chemokines/cytokines IL-6, HGF, IL-8, VEGF, and GRO-1 in HNSCC patients with poor outcome suggests that interrupting this pathway would have therapeutic value. Neutralizing antibodies to HGF and small-molecule inhibitors to its receptor, c-Met, are currently ongoing early-phase testing as anticancer agents. IL-6 is known to induce HGF (28, 29), which activates c-Met. C-Met in turn can induce the expression of VEGF, IL-8, and GRO-1 (30, 31). Blocking HGF or inhibiting c-Met would abrogate the effect of IL-6 on HGF expression and in turn prevent the induction of VEGF, IL-8, and GRO-1. This might be an effective targeted therapeutic strategy in patients with evidence of overactivity of this pathway.

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