Dissecting responsive phenotypes through cytokine and angiogenic factor analysis

Renal cell carcinoma (RCC), long considered influenced by the host immune environment, is also now recognized as driven by tumor-associated angiogenesis from overproduction of vascular endothelial growth factor (VEGF). These biologic underpinnings have lead to therapeutics directed historically toward augmentation of an antitumor immune response and more recently to VEGF inhibition [1]. Although the majority of metastatic RCC patients will have some degree of tumor burden reduction and ~11 months of initial disease control, resistance appears inevitable, either primarily or after a period of initial response. In addition, several treatment options in metastatic RCC, including immunotherapy, VEGF-targeted therapy, as well as inhibition of mammalian target of rapamycin, have fueled interest in developing predictive biomarkers to guide treatment choices.

Initial attempts to predict patient outcome have focused on clinical features. Several schemas of clinical parameters can identify patient characteristics associated with a more favorable clinical outcome [2, 3]. These schemas, however, are prognostic and not likely predictive in that they incorporate similar characteristics as those developed in the cytokine era. Thus, they are not specific to targeted therapy but rather reflect the variable natural biology and growth rate of metastatic RCC and identify patients with a more indolent disease course regardless of treatment. Thus, while these schemas are associated with outcome after treatment, they do not at present allow for specific treatment selection. Molecular features have also been examined in relation to clinical outcome with VEGF-targeted therapy. Obvious markers relating to the VEGF pathway [e.g., von Hippel-Lindau (VHL) mutation, VEGF/soluble VEGF receptor levels, etc.] have not shown utility as predictive biomarkers [4, 5]. Toxicity of therapy has also been studied. Most notably, treatment-induced hypertension has been shown to be associated with clinical outcome across a variety of VEGF-inhibiting approaches and a wide array of diseases including RCC [6–9]. The biology and potential mechanisms behind this association are not well understood, and by definition, this phenomenon is observed after therapy initiation. Thus, the optimal strategy to use this observation in clinical practice awaits further prospective study.

Upon this landscape of biomarker efforts, Zurita et al. [10] have analyzed circulating cytokines and angiogenic factors (CAF) as a correlate to a small randomized trial of a VEGF receptor inhibitor, sorafenib, versus sorafenib plus low-dose interferon in metastatic RCC patients. The authors note the inconsistent results with prior analyses of single circulating proteins and thus have analyzed multiple CAF relevant to angiogenic and immune pathways in an attempt to characterize the phenotype of patients inherently responsive or resistant to one or the other treatment approach. A group of patients with relatively higher expression of pro-angiogenic and hypoxia-regulated factors was differentiated from a group with relative overexpression of interleukins and other proinflammatory factors. Most notably, the authors then constructed a CAF ‘index’ using 6 of 52 measured factors and differentiated based on this index patients with a greater benefit from VEGF receptor inhibition alone versus greater benefit with VEGF receptor inhibition in combination with interferon. A similar analysis of CAF has been undertaken by the author’s group in metastatic RCC patients receiving the VEGFR inhibitor, pazopanib [11]. Analysis of CAFs from metastatic RCC patients on the phase III trial of pazopanib versus placebo identified a seven-factor signature including interleukin 6, interleukin 8, hepatocyte growth factor, osteopontin, TIMP1, VEGF and E-selectin. A differential effect on the outcome depending on factor expression was seen in both the placebo (P = 0.0005, signature high expression versus low, 11 versus 24 weeks) and the pazopanib arms (P = 0.001, high 25 versus low 48 weeks). Thus, this analysis was unable to completely separate prognostic versus predictive CAFs. In addition, it appears that a common identified factor, osteopontin, had the opposite influence on relative outcome to pazopanib versus sorafenib (albeit with different comparator arms). This, in addition to the fact that mostly nonoverlapping CAFs were identified as associated with outcome, underscores either the different biology of response to different VEGF receptor inhibitors or more likely the limitations of analysis of a large number of factors on relatively small sample sets.

The immediate clinical value of these data are limited as the clinical trial did not report significant differences between the arms and combination therapy with sorafenib and interferon remains investigational. Additional limitations include the lack of correction for multiple comparisons and that no accepted clinical characteristics such as performance status were associated with progression-free survival. Nonetheless, the authors are to be congratulated for this effort to identify patients with differential benefit from separate treatments. The exact biology behind the associated CAF index components and differential response to therapy also is not well characterized. For example, the role of osteopontin in the biology of response or resistance to either VEGF-targeting therapy or immunotherapy is not obvious. Nonetheless, this work is representative of the type of analysis...
needed to advance biomarker development in RCC. Analysis of multiple aspects of tumor biology in a prospective randomized trial is critical. Furthermore, validation in a large independent dataset is required as is a greater understanding of the biology of specific components of this profile. These data represent a small step toward the goal of clinical biomarkers, which is to identify a susceptible subset of patients in whom the risk/benefit ratio of therapy can be favorably altered by the targeted application of a specific treatment.

B. Rini*
Cleveland Clinic Taussig Cancer Center, Cleveland, USA
(*E-mail: rinib2@ccf.org)

disclosure
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