RENAL CELL CARCINOMA IN FOCUS

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Prognostic Factors in Patients Treated With VEGF-targeted Therapies

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H&O What are the clinical response rates for patients with metastatic renal cell carcinoma (RCC) who are treated with vascular endothelial growth factor (VEGF) therapy?

TC Among the several VEGF-targeted therapies that are currently approved by the U.S. Food and Drug Administration (FDA), the response rate ranges from approximately 10% to 47%, depending on the agent. With bevacizumab (Avastin, Genentech) or sorafenib (Nexavar, Bayer Healthcare), the rate would be approximately 10%; with pazopanib (Votrient, GlaxoSmithKline), a new agent recently approved by the FDA, the rate is approximately 30%; the rate for sunitinib (Sutent, Pfizer) is known to be up to 47%. Here, response rate means RECIST-refined response rate, which is defined as at least a 30% decrease in the sum of the largest diameters of the target lesions. This parameter is a method used more in clinical trials and less in clinical practice. Also, some patients experience some minor tumor shrinkage (<30%) that does not qualify them for a "response," but nevertheless they stay on therapy for a prolonged period of time. We are estimating that there are several other agents that may be on their way to FDA approval in the next couple of years.

H&O What factors appear to influence patient outcome to VEGF-targeted agents?

TC The clinical endpoint that we have mostly focused on was overall survival (OS). Several studies found that what differentiates these patient outcomes are baseline clinical (eg, performance status) and laboratory (eg, presence of baseline anemia) parameters at therapy initiation. These patients can be grouped into several prognostic categories—poor, intermediate, and good—depending on the number of prognostic factors in each group.

It is important to stress that all these factors are not considered to be "predictive," which means they do not predict a certain response to therapy. Prognostic factors tell us about the natural history of the disease in a particular context, such as patients treated with VEGF-targeted agents, not what type of effect we will see when a particular intervention has taken place. The same can be said about predicting development of resistance to therapy. Perhaps, patients who respond poorly to VEGF-targeted therapy or to cytokines have an intrinsic resistance to therapy and should be given other therapies. However, these factors do not specifically tell us that these patients are resistant to that particular therapy; patients may have an inherently unfavorable characteristic independent of therapy.

H&O What is the effect of VHL gene status on clinical objective response?

TC The focus on the VHL gene status and its correlation with outcome came from background data that suggested that patients who have an aberration in the VHL gene of the kidney tumor may produce more VEGF, and therefore, in theory, may benefit more from VEGF-targeted therapy. In our work, we found that there may be an increased response to VEGF-targeted therapy depending on the type of mutation; we found in a multivariate analysis that patients with mutations that are predicted to truncate the VHL gene may respond better to VEGF-targeted therapy; however, this did not translate into an improved survival

in terms of progression-free survival (PFS) or OS. Other investigators, such as Hutson and colleagues, confirmed our findings that VHL mutation does not predict for PFS.

H&O Can you describe future prognostic models?

TC Currently, the Memorial Sloan-Kettering Cancer Center (MSKCC) model is the most widely used prognostic model. In this model, adverse prognostic factors include an interval from diagnosis to treatment of less than 1 year, Karnofsky performance status less than 80%, serum lactate dehydrogenase greater than 1.5 times the upper limit of normal, corrected serum calcium greater than the upper limit of normal, and serum hemoglobin less than the lower limit of normal.

It is important to note that these prognostic risk profiles are derived from an era of immunotherapy and are limited to a patient population that is only eligible for participating in immunotherapy clinical trials. Wondering if the same prognostic factors are relevant to patients treated with VEGF-targeted therapy, and as part of an international collaboration, we had assessed 564 patients who had received VEGF-targeted therapy and proposed a model that may be more reflective of the current standard of care (Table 1).

The model is composed of 2 clinical and 4 laboratory values that are readily available and that have been demonstrated to be associated with adverse outcomes. This 6-factor model is associated with a C-index of 0.73, which is comparable to or slightly better than that of other published models in the era of targeted therapy (C-index, 0.63).

The goal was to create a simple clinical-prediction model that would be applicable to the general patient with metastatic RCC who was treated with VEGF-targeted therapy; our hope was to allow the stratification of such patients into favorable, intermediate, and poor prognosis groups.

H&O How will the identification of such prognostic factors affect patient care?

TC The identification and further understanding of prognostic factors will be significant for clinical trials, patient counseling, and knowing what we are dealing with, because not every advanced RCC case is the same.

Also, in the future, I believe that it will become extremely important to integrate not only clinical but also molecular prognostic factors in the same nomogram or prognostic model. A variety of molecular markers have been assessed in patients with metastatic RCC, including chromosomal abnormalities, expression of various hypoxia-related molecules, carbonic anhydrase IX (CAIX), p53, phosphatase and tensin homolog deleted from chromosome 10 (PTEN), and vimentin, and were found to be independent prognostic factors for survival. Although none of the molecular markers have been shown to be of such major independent importance that it trumps any clinical prognostic factor at this time, the value of molecular markers as independent prognostic factors should be further investigated, especially in relatively homogeneous groups of patients (eg, mRCC patients who have been treated with VEGF-targeted therapy), and in conjunction with the classic prognostic factors.

Table 1. Multivariable Analysis and Final Model

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P* Value
Clinical				
KPS <80%	0.92 ± 0.14	2.51	1.92–3.39	<.001
Time from diagnosis to treatment <1 year	0.35 ± 0.13	1.42	1.09–1.84	.0098
Laboratory				
Hemoglobin <LLN	0.54 ± 0.14	1.72	1.31–2.26	.001
Calcium >ULN	0.59 ± 0.17	1.81	1.29–2.53	.0006
Neutrophil count >ULN	0.88 ± 0.17	2.42	1.72–3.39	<.0001
Platelet count >ULN	0.40 ± 0.16	1.49	1.09–2.03	.0121

Total number of patients=564.

CI=confidence interval; SE=standard error; KPS=Karnofsky performance status; LLN=lower limit of normal; ULN=upper limit of normal.

Suggested Readings

Bukowski RM. Prognostic Factors for Survival in Metastatic Renal Cell Carcinoma. *Cancer.* 2009;2273-2281.

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Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009;27:5794-5799.