

Prognostic biomarkers for patients with advanced renal cell carcinoma treated with VEGF-targeted tyrosine kinase inhibitors

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Abstract: Tyrosine kinase inhibitors with activity against vascular endothelial growth factor receptor 2 are now standard treatment for the majority of patients with advanced renal cell carcinoma. The clinical development of these agents followed by their broad clinical utilization has allowed the creation of large databases to facilitate the identification of prognostic biomarkers and development of prognostic models. While several clinical prognostic models have been created, work continues on identifying novel biomarkers which might be used in conjunction with or even in place of these clinical models. In this review, we discuss the progress thus far in improving on current prognostic models and speculate on possible developments in the near future.

Keywords: renal cancer, prognostic biomarker, VEGF tyrosine kinase inhibitors

Introduction

Within recent years, receptor tyrosine kinase inhibitors (TKI) directed against vascular endothelial growth factor (VEGF) signaling have been established as standard of care for the majority of patients with advanced renal cell carcinoma of clear cell histology. Currently, four TKI with activity against VEGF receptor 2 (VEGFR2) are approved by the United States Food and Drug Administration and widely administered to patients with advanced renal cell carcinoma. This broad clinical experience has allowed the creation of large databases which have facilitated the exploration of prognostic factors specific to patients treated with these agents. In this review, we discuss the current status of these prognostic biomarkers and their potential utility in both patient care and clinical investigation.

Prognostic versus predictive biomarkers

A biomarker is a measurable characteristic which can be an indicator of a biologic process, both normal and pathologic. In oncology, biomarkers are most frequently used to indicate clinical events, such as disease onset, recurrence, response to therapy, or survival. A prognostic biomarker relates to the natural history of the underlying cancer independent of therapy, whereas predictive biomarkers reflect the likelihood of differential responses to certain interventions. With respect to patients specifically treated with VEGF-targeted TKI, the distinction becomes murkier. In principle, prognostic factors are those which reflect the likelihood of clinical outcomes such as disease control (progression-free survival) or overall survival regardless of whether the patient is actually treated with a VEGF-targeted agent or not. In contrast, a truly predictive biomarker reflects the likelihood of similar clinical outcomes in patients who

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are actually treated and may not have relevance in patients who are not treated. Because the establishment of a biomarker as predictive typically requires concurrent validation in a control group, the vast majority of biomarkers studied in renal cell carcinoma thus far must be considered prognostic and we focus on these in this review.

Clinical and laboratory-based prognostic factors

A multitude of clinical and laboratory-based factors have been identified as having prognostic value in patients with renal cell carcinoma. These factors have included the presence of constitutional symptoms, poor performance status, markers of inflammation such as erythrocyte sedimentation rate or C-reactive protein, measures of tumor burden, elevated lactate dehydrogenase, hypercalcemia, anemia, and thrombocytosis. Many of these factors have been incorporated into prognostic models through multivariate analysis. For patients with all stages of renal cell carcinoma, perhaps the best known of these models are the University of California Los Angeles integrated staging system and the Mayo Clinic metastases-free survival scoring system.^{1,2} The University of California Los Angeles integrated staging system integrated several tumor-based factors, such as tumor-node-metastasis stage, Fuhman's grade, and Eastern Cooperative Oncology Group performance status, into a prognostic model for survival in patients undergoing nephrectomy. The Mayo Clinic metastases-free survival scoring system integrates tumor stage, regional lymph node status, tumor size, Fuhrman's nuclear grade, and presence of tumor necrosis into a prognostic model for the risk of developing metastases in patients undergoing nephrectomy.

While these two models are useful for prognosis in patients undergoing nephrectomy, the best known prognostic model for patients with metastatic disease is that developed at the Memorial Sloan Kettering Cancer Center. This model groups patients into favorable, intermediate-risk, and high-risk groups based on the presence of risk factors including low Karnofsky performance status, high lactate dehydrogenase, elevated serum calcium, low hemoglobin, and absence of prior nephrectomy.³ This model was later modified to be specific to treatment with interferon- α and included the same risk factors with the exception of the absence of prior nephrectomy, which was replaced with a time from diagnosis to treatment of less than one year.⁴

Although the Memorial Sloan Kettering Cancer Center model also appears to be valid in the TKI era,⁵ many other prognostic models have been developed or are specific for patients treated with VEGF-targeted agents. Although these models are described in Table 1, one model deserves special note because it has recently been externally validated. Heng et al originally reported the findings of the International Metastatic Renal Cell Database Consortium in 2009 in a study of 645 patients with treatment-naïve metastatic renal cell carcinoma who underwent therapy with a VEGF-targeted agent.⁶ The investigators identified six independent prognostic factors for overall survival in this group of patients: anemia (hemoglobin less than the lower limit of normal); hypercalcemia (corrected calcium greater than the upper limit of normal); Karnofsky performance status less than 80%; time from diagnosis to treatment of less than one year; neutrophilia (neutrophil count greater than the upper limit of normal); and thrombocytosis (platelet count greater than the upper limit of normal). Patients were then

Table 1 Three models used for prognostic prediction based on risk factors in patients with renal cell carcinoma

Prognostic model	Risk factors	Prognostic prediction
Cleveland Clinic Foundation ⁹	Interval from diagnosis to treatment <2 years Baseline corrected serum calcium <8.5 mg/dL or >10 mg/dL ECOG performance status >0 Neutrophil count >4.5 × 10 ⁹ /L Platelet count >300 × 10 ⁹ /L	0–1 risk factors, median PFS 20.1 months 2 risk factors, median PFS 13 months ≥3 risk factors, median PFS 3.9 months
International Kidney Cancer Working Group ¹⁰	Prior treatment, performance status, number of metastatic sites, time from diagnosis to treatment, hemoglobin, white blood count, lactate dehydrogenase, alkaline phosphatase, and serum calcium	Favorable: median survival 26.9 months Intermediate: median survival 11.5 months Poor: median survival 4.9 months
International Renal Cell Carcinoma Database Consortium ^{6,7}	Karnofsky performance status <80% Less than one year from diagnosis to treatment Anemia Hypercalcemia Neutrophilia Thrombocytosis	0 risk factors: median OS 43.2 months 1–2 risk factors: median OS 22.5 months ≥3 risk factors: median OS 7.8 months

Abbreviations: ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival.

identified as having a favorable (no risk factors), intermediate (1–2 risk factors), or poor (\geq three risk factors) prognosis. In the independent validation of this model in 1028 patients treated with first-line VEGF-targeted agents, the median overall survival associated with these prognostic groups was 43.2 months, 22.5 months, and 7.8 months, respectively.⁷ The prognostic model of the International Metastatic Renal Cell Database Consortium is currently the only externally validated model specific for patient undergoing first-line therapy with VEGF-targeted agents and therefore will likely become the standard model for risk stratification in both clinical decision-making and clinical trials.

In contrast with the first-line setting, prognostic factors for patients receiving VEGF-targeted TKI as second-line therapy are less established. As a continuation of their initial report of the International Renal Cell Database Consortium, Vickers et al reported that a higher baseline Karnofsky performance score prior to first-line therapy predicted a greater likelihood of receiving a second-line therapy.⁸ While many groups have suggested that progression-free survival with first-line VEGF-targeted TKI is not predictive of response to a second VEGF-targeted TKI, it may be prognostic with respect to progression-free survival on second-line therapy.^{9–12} Ultimately, however, it is not clear that second-line and further therapy alters the prognosis established in the first-line setting.

Clinical pharmacodynamic markers

While most prognostic models have utilized baseline clinical factors, it is becoming increasingly clear that similar prognostic information may be gained from pharmacodynamic changes in response to treatment. As a therapeutic class, antagonists of VEGF signaling produce a number of characteristic mechanism-based toxicities. The correlation of the occurrence of these toxicities with clinical outcomes has been rigorously studied throughout the clinical development of the VEGF-targeted TKI. The most solidly established toxicity with respect to prognosis appears to be the development of hypertension. In a small retrospective analysis of adverse events experienced in 32 patients as a result of sunitinib treatment versus response, Rixe et al reported that only the occurrence or worsening of hypertension was associated with improved clinical response.¹³ In larger pooled analysis of 544 patients treated with sunitinib, Rini et al reported that patients who developed treatment-related systolic hypertension has superior outcomes compared with those who did not with respect to objective response rate (54.8% versus 8.7%), median progression-free

survival (12.5 versus 2.5 months), and overall survival (30.9 versus 7.2 months).¹⁴ This concept was also validated retrospectively for axitinib through a secondary analysis of the Phase III trial of axitinib versus sorafenib in patients with previously treated renal cell carcinoma.¹⁵ The value of dose titration until hypertension is currently being assessed prospectively in a randomized double-blind Phase II trial of axitinib in patients with advanced renal cell carcinoma (NCT00835978). While there is little doubt that treatment-related hypertension is a prognostic factor for patients treated with VEGF-targeted TKI, the wide adoption of the practice of dose titration until hypertension is observed with these agents will likely significantly diminish its value as a distinguishing marker.

Blood-based biomarkers

Throughout the clinical development of VEGF-targeted TKI, blood has provided a convenient source of potential biomarkers. The ease of collection of specimens and measurement has led to the observation that a multitude of circulating factors are modulated by treatment with VEGF-targeted agents. Many of these circulating factors have been studied in the context of large clinical studies and have shown promise as prognostic biomarkers.

Not surprisingly, much of the early work on circulating biomarkers focused on the various VEGF and VEGF receptor isoforms. Rini et al first reported that baseline circulating levels of soluble VEGF receptor 3 (VEGFR3) and VEGF-C levels may be prognostic of progression-free survival in response to treatment with sunitinib.¹⁶ Higher circulating levels of VEGF-A were also shown to be associated with lower overall survival in both the treatment and placebo groups of the Phase III TARGET trial of sorafenib versus placebo.¹⁷ A higher baseline VEGF-A level was also correlated with shorter progression-free survival in either arm of the Phase III AVOREN trial comparing bevacizumab plus interferon with interferon alone.¹⁸ Finally, baseline circulating VEGF-A levels were recently shown to be prognostic of overall survival but not predictive of benefit from treatment in four separate Phase III trials of bevacizumab in renal cell, colorectal, and lung carcinoma.¹⁹

In addition to VEGF, many other soluble prognostic biomarkers have been identified. For example, a subsequent analysis of the TARGET study showed that plasma levels of tissue inhibitor of metalloproteinase-1 was an independent prognostic biomarker for overall survival.²⁰ Another recent study has suggested that a higher serum C-reactive peptide level is an independent prognostic factor for shorter

progression-free survival and overall survival in patients treated with sunitinib.²¹ One of the most widely corroborated circulating biomarkers is serum interleukin-6. Several studies have shown that serum interleukin-6 is an independent prognostic marker for progression-free and overall survival in patients with metastatic renal cell carcinoma.^{18,22,23} An analysis of plasma cytokines and angiogenic factors in blood collected from patients as part of Phase III trials of pazopanib confirmed that higher baseline interleukin-6 levels, along with those of interleukin-8 and osteopontin, were prognostic for a shorter progression-free survival.²⁴ Interestingly, within the study population, these same factors were prognostically stronger than Eastern Cooperative Oncology Group performance status and prognostic systems based on clinical factors, such as those from the Memorial Sloan Kettering Cancer Center and the International Renal Cell Database Consortium. Higher baseline interleukin-6 levels were also found to be predictive of a progression-free survival benefit from treatment with pazopanib compared with placebo. Interleukin-6 is now being proposed for prospective assessment as a predictive biomarker in clinical trials.

Efforts are ongoing to identify other markers in the blood besides circulating cytokines and angiogenic factors. Many groups have focused on potentially novel biomarkers such as circulating endothelial cells or circulating tumor cells. While these remain biologically enticing given the mechanism of action of VEGF-targeted TKI, the paucity of these types of cells in the circulation has made their detection and assessment extremely difficult thus far and a major technical limitation. In the meantime, however, consideration must be given to incorporating the more widely studied blood-based markers, particularly VEGF-A and interleukin-6, into the more established clinical models to strengthen their potential prognostic value.

Tissue-based models

Like the blood-based biomarkers, many of the most rigorously explored tissue-based prognostic biomarkers for patients treated with VEGF-targeted TKI are related to the mechanism of action of this class of agent. The majority of clear cell renal cell carcinoma are characterized by bi-allelic dysfunction of the von Hippel-Lindau (*VHL*) gene, resulting in inappropriate accumulation of hypoxia-inducible factor (HIF)-1 α and HIF-2 α , with subsequent activation of their downstream genes, including those for VEGF and platelet-derived growth factor (PDGF). Because the TKIs approved for the treatment of renal cell carcinoma all share activity against VEGFR2

and PDGF receptor (PDGFR)- β , it is not surprising that many investigators have studied the correlation between *VHL* loss and outcomes in patients treated with these agents. In the largest such analysis including tumor specimens and outcomes from 123 patients treated with VEGF-targeted therapy, Choueiri et al reported that patients whose tumor specimens showed a loss of function mutation in *VHL* had a response rate of 52% versus 31% in wild-type patients, and that loss of function mutation was an independent prognostic factor for improved response on multivariate analysis.²⁵ However, these findings must be validated in a larger patient population before their incorporation into existing prognostic models.

Many investigators have expanded upon genetic analysis to include studies of polymorphisms and chromosome copy numbers. For example, Bianconi et al recently reported that certain single nucleotide polymorphisms in VEGF or VEGFR may predict benefit from treatment with either sunitinib or pazopanib.²⁶ Similarly, Jonasch et al have reported their finding that chromosomal copy number variation may provide prognostic information in patients treated with VEGF-targeted agents.²⁷ Specifically, gain of 8q and loss of 16q, 20p, or 20q were associated with a shorter overall survival, while gain of 1q and 5q was associated with longer overall survival. Currently, these studies remain preliminary and must be validated prospectively in larger patient samples.

In addition to genetic analysis, many biomarkers have been investigated based on expression as determined by immunohistochemistry. Patel et al reported that high expression of both HIF-1 α and HIF-2 α in renal cell carcinoma specimens was correlated with a higher likelihood of objective response to sunitinib.²⁸ Despite these findings, these results have not been able to be reproduced across larger patient populations and across different VEGF-targeted agents. It is possible that broad application of this marker is limited by technical considerations, such as the lack of an antibody against HIF-1 α and HIF-2 α which can reliably and reproducibly detect expression across different tissue specimens. Despite these technical limitations, variable expression of the HIFs remains a potentially interesting biomarker worthy of further investigation.

In addition to expression of HIF itself, other investigators have focused on expression of gene products regulated by HIF. One such gene regulated by HIF-1 α which has been investigated extensively in renal cell carcinoma is carbonic anhydrase IX, a surface transmembrane enzyme believed to be responsible for maintaining an acidic extracellular pH.

Carbonic anhydrase IX expression can be detected in up to 90% of renal cell carcinoma specimens, and its expression has been shown to be inversely correlated with both overall survival and likelihood of developing metastases.²⁹ Therefore, carbonic anhydrase IX expression may have value as both a diagnostic and prognostic marker in early-stage renal cell carcinoma. Unfortunately, studies thus far have failed to establish the prognostic or predictive value of carbonic anhydrase IX expression with respect to VEGF-targeted TKI.^{30,31} Overall, while immunohistochemical analysis has identified several interesting biomarkers, this approach remains limited by technical considerations, such as reliance on availability of reliable antibodies, stability of epitopes, and an inherent subjectivity in interpretation.

Novel biomarkers

Although a multitude of biomarkers are under exploration in renal cell carcinoma using various technology platforms, several recently identified genetic alterations in renal cell carcinoma are worthy of special attention in the coming years with respect to prognosis in patients treated with VEGF-targeted TKI. Results of both targeted and unsupervised sequencing studies in renal cell carcinoma have recently shown that several genes which function in histone modification and chromatin remodeling are frequently mutated in clear cell renal cell carcinoma, including *PBRM1*, *BAP1*, *SETD2*, *KDM5C*, and *ARID1A*.^{32–36} The most commonly mutated of these is *PBRM1*, which encodes the BAF180 protein, a member of the PBAF SWI/SNF chromatin remodeling complex. Truncating mutations in *PBRM1* have been described in up to 41% of clear cell renal cell carcinomas.³² *BAP1*, which encodes a nuclear deubiquitinase, has also recently been shown to be inactivated by bi-allelic alteration in up to 15% of clear cell renal cell carcinomas.³³ Likewise, *SETD2*, which encodes a histone methyltransferase, is mutated in approximately 8% of clear cell renal cell carcinomas.³⁴ Not surprisingly, correlation of the presence of these mutations with clinical outcomes is already providing prognostic information. In a recently published analysis, Hakimi et al³⁶ were able to show that patients whose tumors possessed mutations in *PBRM1*, *BAP1*, *SETD2*, or *KDM5C* were more likely to present with advanced stage and grade. Similarly, Kapur³⁷ et al showed that patients whose renal cell carcinoma possessed mutations in *BAP1* had a significantly shorter overall survival than those whose renal cell carcinoma possessed mutations in *PBRM1*. These authors also identified a smaller subset of patients, ie, those whose renal cell carcinoma contained mutations of both *BAP1* and *PBRM1*, who had a particularly shorter overall survival.

Although work correlating the presence of these mutations with clinical outcomes in patients treated with VEGF-targeted TKI has not yet been published, such analysis is ongoing. It is hoped that the mutational data on these chromatin remodeling and histone modifying genes, in conjunction with loss of *VHL*, might provide valuable prognostic and predictive information which can be incorporated into the established clinical models to not only stratify patients in clinical trials but also potentially guide therapeutic decisions.

Conclusion

Tremendous progress has been made in creating and optimizing clinical prognostic models. Efforts are ongoing to identify novel biomarkers which might be used in conjunction with or possibly even in place of the current clinical models. While several promising markers such as serum VEGF-A and interleukin-6 have emerged, these markers must be validated prospectively and independently before they can be adopted into clinical use. At the same time, identification of novel genes which are frequently mutated in renal cell carcinoma suggests that a new, largely genetic classification scheme for renal cell carcinoma may be emerging. Although this must be considered conjecture at this point, a new classification scheme might have major prognostic implications with respect to not only VEGF-targeted therapies but other treatment modalities across renal cell carcinoma as well.

Disclosure

The author reports no conflicts of interest in this work.

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