Predictive Markers in Advanced Renal Cell Carcinoma

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Predictive markers of response to therapy are increasingly important in advanced renal cell carcinoma (RCC) due to the proliferation of treatment options in recent years. Different types of potential predictive markers may include clinical, toxicity-based, serum, tissue, and radiologic biomarkers. Clinical factors are commonly used in overall prognostic models of RCC but have limited utility in predicting response to therapy. Correlation between development of particular toxicities and response to therapy has been noted, such as the correlation between hypertension and response to angiogenesis-targeted therapy. Serum and tissue biomarkers will be covered in detail elsewhere, but factors such as serum lactate dehydrogenase (LDH) and circulating cytokines show promise in this regard. Finally, baseline or early treatment radiology studies may have predictive ability for longer term efficacy, with most studies to date focusing on functional imaging modalities such as positron emission tomography (PET) scans, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), and DCE ultrasound (US). The ultimate goal of developing predictive biomarkers is to enable rational and personalized treatment strategies for patients with advanced RCC.
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The explosion of therapeutic options for the treatment of advanced renal cell carcinoma (RCC) has made patient selection more important that ever. Different classes of treatment options include angiogenesis-directed therapy, mammalian target of rapamycin (mTOR)-directed therapy, immunotherapy, and others. Responses to each of these classes of treatment, and to individual drugs within each class, are widely variable, with some patients having marked and durable responses, and others having little or no apparent response. Baseline or early predictive factors that would rationally guide selection of therapy in individual patients are therefore of great interest.

It is important to distinguish prognostic markers, which provide information about patient outcome independent of any specific intervention, from predictive markers, which provide information about outcome specifically related to a particular intervention.[1] Potential predictive markers include tissue- or serum-based biomarkers, radiographic-based markers, and clinical markers. Tissue and serum biomarkers are addressed elsewhere in this issue of *Seminars in Oncology*. We will focus here on radiographic and clinical predictive markers of disease response in RCC.

PREDICTIVE CLINICAL MARKERS

To some extent, clinical characteristics of patients are used in guiding selection of therapy. Risk stratification criteria that distinguish good-, intermediate-, and poor-risk patients with metastatic RCC (mRCC) are routinely considered in decision-making regarding whether to treat, and if so with which agent(s).[2–5] The stratification criteria are, for the most part, prognostic factors, which provide information about outcome that is independent of intervention. However, the inclusion of these criteria into clinical trial design has resulted in practice guidelines that reflect these criteria in treatment selection as well. In contemporary practice, most patients with good- or intermediate-risk mRCC begin therapy with angiogenesis-targeted agents such as sunitinib, pazopanib, or others, which inhibit the vascular endothelial growth factor (VEGF) pathway. In contrast, patients with poor-risk mRCC are generally treated initially with the mTOR-directed therapy, temsirolimus. As new agents are

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developed and studied, careful attention to risk criteria is essential in helping to define target populations.

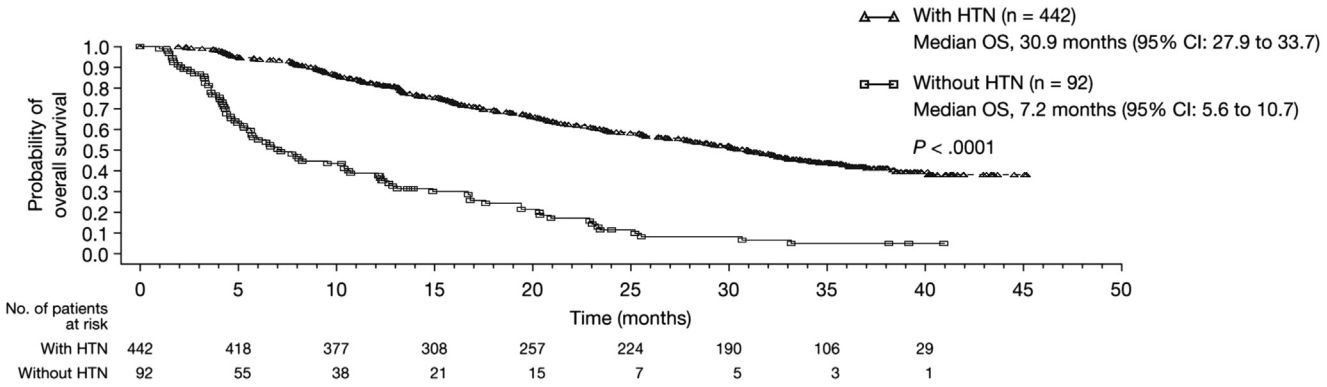
A commonly used system is the Memorial Sloan-Kettering Cancer Center (MSKCC) classification developed originally in the cytokine era. The pretreatment adverse prognostic factors in this system include diminished Karnofsky performance status (< 80%), high lactate dehydrogenase (LDH) levels (> 1.5 times upper limit of normal [ULN]), low hemoglobin levels, high corrected serum calcium levels (> ULN), and absence of prior nephrectomy. Patients with none of these factors are deemed good risk, those with 1–2 are deemed intermediate risk, and those with 3 or more adverse factors are poor risk.[5]

A similar but modified prognostic model has been developed based on patients treated with VEGF-targeted therapy. Heng and colleagues identified six adverse prognostic factors including diminished Karnofsky performance status (< 80%), low hemoglobin levels, high corrected serum calcium levels, time from diagnosis to treatment < 1 year, neutrophil count greater than ULN, and platelets greater than ULN.[3] As with the MSKCC criteria, patients with none of these factors are considered good risk, those with 1–2 are deemed intermediate risk, and those with 3 or more adverse factors are poor risk. It is notable that the median survival of each group has positively shifted substantially from the MSKCC to the Heng criteria, perhaps reflecting overall survival (OS) gains in the era of targeted therapy. The good-risk group had median survival of 20 months, the intermediate-risk group 10 months, and the poor-risk group 4 months in the MSKCC study; in contrast, in the Heng study, the good-risk group median survival had not been reached with more than 2 years of follow-up, the intermediate risk group had median survival of 27 months, and the poor-risk group 8.8 months.[3,5]

TOXICITY AND EFFICACY: POTENTIAL CORRELATIONS

Beyond the criteria described above, clinical characteristics have not been used to rationally guide patient selections for particular therapy in a systematic way. One intriguing possibility is that readily apparent adverse effects might provide early and reliable indications of drug effect. To that end, following the development of many of the targeted agents for mRCC, careful retrospective analysis has been done to assess whether the development of particularly adverse effects correlated with eventual positive response to therapy. The best characterized of these is the likely association between hypertension and efficacy in response to angiogenesis-targeted therapy.

In a retrospective study of patients with mRCC treated with sunitinib, development of hypertension was positively associated with response rate, progression-free survival (PFS) and OS.[6] The PFS and OS among those patients who developed hypertension were 12.5 months and 30.9 months, respectively, compared with 2.5 months and 7.2 months in those who did not develop hypertension (Figure 1). Clinically important adverse events related to hypertension were similar in the two groups. This and other studies have shown that appropriate clinical management of hypertension does not reduce efficacy of angiogenesis-targeted therapy.[7,8] Other angiogenesis-targeted drugs, such as bevacizumab, sorafenib, and axitinib, also have shown evidence of association between hypertension and efficacy in RCC, as well as in other tumor types.[9–12] The mechanism behind this association is not clear, and the possibility exists that development



	With HTN			Without HTN		
Month	N	S	95% CI	N	S	95% CI
10	377	86.3	(82.7 to 89.2)	38	43.5	(33.0 to 53.5)
20	257	66.3	(61.5 to 70.6)	15	21.4	(13.1 to 31.0)
30	190	51.9	(46.9 to 56.7)	5	8.2	(3.2 to 16.1)

Figure 1. Association of development of hypertension (HTN) and overall survival (OS).