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Treatment Selection for Patients With Metastatic Renal Cell Carcinoma

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Abstract

The availability of approved agents with distinct mechanisms of action has encouraged investigations to identify optimal treatment strategies for specific patients and specific tumor features. Study of tumors from patients treated with interleukin 2 (IL-2) has suggested that response was unlikely in patients with tumors with papillary features or low carbonic anhydrase IX (CAIX) expression. A model combining histologic features and CAIX expression separated patients into 2 groups of roughly equal size, with 96% of the responding patients being in the favorable prognostic group. Additional studies have begun to identify molecular features that might predict response IL-2 therapy. In contrast, clinical trial data suggest that temsirolimus was relatively more active than interferon in patients with tumors containing non-clear cell features. Furthermore, pathologic examination showed no correlation of response with CAIX expression but an apparent association with high expression of either phospho-AKT or phospho-S6, proteins either upstream or downstream of mTOR. Preliminary investigations of tumor specimens from patients receiving VEGF-targeted therapy suggested that high hypoxia inducible factor expression might predict for response. In addition, response appeared more likely in tumors with mutated or methylated *VHL* genes; however, substantial antitumor activity was still seen in patients with *VHL* wild-type tumors, particularly in patients treated with either sunitinib or axitinib, rather than bevacizumab or sorafenib. Although these data provide some guidance in treatment selection, considerably more research is needed to identify and validate selection models for particular treatment approaches and enable rational and optimal utilization of the available treatment options.

Keywords

renal cell carcinoma; immunotherapy; antiangiogenic therapy; TOR inhibitors; treatment selection

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Introduction

The availability of approved agents with distinct mechanisms of action (immunotherapy, vascular endothelial growth factor [VEGF] pathway, and mTOR inhibitors) has complicated treatment decisions for patients with advanced kidney cancer. Although randomized phase 3 trials can provide guidance for the average patient in a specific clinical situation, individual patients and tumors have distinct characteristics that may greatly influence their response to different treatments. Identifying the optimal treatment for a particular patient has become an important goal of current investigation.

Recent clinical trials have focused on either front-line or cytokine refractory patients and have been stratified by clinical prognostic factors developed by Motzer et al1 from patients treated with interferon (IFN) alfa. Taken together, these studies have led to the creation of an "evidence-based" algorithm (Table 1) for treatment selection, with sunitinib or bevacizumab plus IFN being favored for front-line therapy in patients with good or intermediate prognosis, temsirolimus being favored for patients with poor prognostic features, sorafenib being favored for patients whose disease has progressed after cytokines, and everolimus being the choice for patients whose disease has progressed after VEGF receptor (VEGFR) inhibitor therapy.2–7 It bears mentioning, however, that the absence of information regarding a particular treatment in a particular patient population is not equivalent to the absence of effectiveness. Furthermore, although treatment selection based on clinical criteria is useful, it is far from ideal. The ultimate goal is to be able to choose treatment strategies that take into consideration the pathologic, molecular, and/or biologic features of the tumor. This article reviews current investigations into predictive biomarkers for immunotherapy, antiangiogenic therapy, and mTOR-targeted therapy in patients with advanced renal cell carcinoma (RCC).

Immunotherapy

Recent phase 3 trials that have established the superiority of regimens that contain sunitinib, temsirolimus, and bevacizumab plus IFN over IFN alfa as front-line therapy for patients with advanced RCC.2,5,8 These studies have clearly limited the role of single-agent IFN in the treatment of this disease. However, a randomized phase 2 trial of sorafenib vs IFN showed similar median progression-free survival (PFS) for the 2 treatments, with IFN therapy performing better than sorafenib for a substantial minority of patients.9 Furthermore, high-dose IL-2 has been shown in 2 randomized phase 3 trials to produce higher response rates and more durable complete responses than lower-dose cytokine regimens.10–12 Thus, cytokine therapy, particularly high-dose intravenous IL-2, remains a reasonable initial treatment option for some patients with metastatic RCC. Correlative biomarker investigations suggest that the potential exists for identifying predictors of response (or resistance) to IL-2 therapy, limiting its use to those most likely to benefit.

Pathology Studies

Responses to immunotherapy are most frequently seen in patients with RCC of the clear cell histologic type.13–15 This observation was detailed in a retrospective analysis of pathology specimens obtained from 231 patients (including 163 primary tumor specimens) who had received IL-2 therapy in Cytokine Working Group clinical trials.13 The response rate to IL-2 was 21% (30 of 146) for patients with clear cell histology in their primary tumors, compared with 6% for patients with non-clear cell histology (1 responder in 17 patients). Among the patients with clear cell carcinoma, response to IL-2 was also associated with the presence of "good" predictive features (eg, more than 50% alveolar and no granular or papillary features) and the absence of "poor" predictive features (eg, more than 50% granular or any papillary features). As a result of these data, it may be appropriate for

patients whose primary tumor is of non-clear cell histology or of clear cell histology but with “poor” predictive features to forgo IL-2-based treatment altogether. However, given that even in the most favorable predictive group more than 50% of patients did not respond to IL-2 therapy, additional investigations into tumor-associated predictors of responsiveness to IL-2 are still necessary.

Immunohistochemistry Studies

Carbonic anhydrase IX (CAIX) has been identified as an immunohistochemical marker that might predict the outcomes of patients with RCC. CAIX is an enzyme whose expression is mediated by the hypoxia inducible factor (HIF) transcriptional complex, which is up-regulated with *VHL* inactivation observed in clear cell RCC.16 This enzyme is thought to regulate intracellular pH during periods of hypoxic stress. CAIX protein is expressed in most RCC specimens but not in normal renal tissue.17,18 In an analysis by Bui et al,17 CAIX expression in more than 85% of tumor cells (high CAIX expression) has been associated with improved survival and a higher objective response rate in IL-2-treated patients. Building on this work, Atkins et al18 developed a 2-component model that combined pathology analysis and immunohistochemical staining for CAIX. In a retrospective analysis, this model was able to identify a “good risk” group that contained 26 (96%) of 27 responders to IL-2 compared with only 18 (46%) of 39 nonresponders (odds ratio, 30; P <.01). A significant survival benefit was also seen for this group (P < .01). The Cytokine Working Group has launched the high-dose IL-2 “Select” Trial to determine, in a prospective fashion, if this model18 can identify a group of patients with advanced RCC who are significantly more likely to respond to high-dose IL-2-based therapy (“good” risk) than a historical, unselected patient population.

Genetic and Gene Expression Studies

Gene expression profiling of tumor specimens to identify patterns of gene expression associated with IL-2 responsiveness may eventually help to further narrow the application of IL-2 therapy to those who will benefit the most. Using this approach, Pantuck et al19 were able to identify a set of 73 genes whose expression distinguished complete responders from nonresponders after IL-2 therapy. In their hands, complete responders to IL-2 have a signature gene and protein expression pattern that includes CAIX, PTEN, and CXCR4. More recent studies with array-based comparative genomic hybridization showed that tumors from complete responders to IL-2 had fewer whole chromosome losses than nonresponders.20 The concentration of losses in sections of chromosome 9p (65% in nonresponders vs 0 in complete responders), which encompass genes for CAIX, pS6, and B7H1, adds some potential mechanistic significance to this observation. Although these results require prospective validation, these approaches may provide powerful tools for clinicians in selecting appropriate treatment options for specific patients and to investigators seeking to understand the molecular biology underlying tumor sensitivity to immunotherapy.

mTOR Inhibitors

Pathologic Features

Although the clinical benefit of high-dose IL-2 may be limited to those patients who have clear cell RCC, this may not be the case with inhibitors of the mTOR pathway. A subsequent analysis of the randomized phase 3 trial of temsirolimus demonstrated that the median overall survival of patients with non-clear cell RCC (75% of whom had the papillary subtype) was 11.6 months in the temsirolimus group vs 4.3 months in the IFN group.21 This differential contrasts with the relatively minor improvement over IFN in patients with clear cell RCC (10.7 months with temsirolimus vs 8.2 months with IFN). The preferential activity of temsirolimus in non-clear cell carcinoma also contrasts with what is seen with the

VEGFR antagonists sorafenib and sunitinib, both of which have only limited activity against these RCC variants.22 These observations suggest that the mechanism of action of mTOR inhibitors may be distinct from those of agents primarily inhibiting VEGFR signaling in the tumor endothelium. During the clinical development of mTOR inhibitors, the antagonism of HIF-1α expression by these drugs has always presented an attractive and logical explanation for their clinical efficacy in RCC.23 However, these recent observations highlight the need for further investigation into the mechanism of action of mTOR inhibitors and the need to identify molecular features that may predict response to these agents.

Predictive Biomarkers

Preliminary efforts to identify such predictive biomarkers have focused on pathologic surrogates of the basal activation status of the presumptive molecular targets of mTOR inhibitors. A small retrospective analysis of pretreatment tumor specimens from a subset of patients with RCC treated with temsirolimus as part of the randomized phase 2 trial24 reported an association of high expression of either phospho-Akt or phospho-S6 ribosomal protein, substrates upstream and downstream of mTOR, respectively, with objective response to temsirolimus.25 In contrast, no apparent correlation was found of CAIX or PTEN expression with response to temsirolimus. A larger analysis of tumor specimens from patients treated with temsirolimus as part of the randomized phase 3 trial also found no correlation between tumor PTEN expression and either tumor response or overall or progression free survival. In addition, no such correlations were observed with baseline HIF-1 a expression26 Although the stability of certain phospho-proteins, in particular phospho-Akt, has been called into question,27 phospho-S6 appears to be a promising potential predictive biomarker for response to mTOR inhibitors, which must be validated through both larger retrospective analysis and prospective studies.

Current and Future Efforts

Future efforts to identify predictive biomarkers of response to mTOR inhibitors must be guided by insights into the mechanism of both response and resistance to mTOR inhibitors. For example, overexpression of eurokaryotic initiation factor 4E (eIF4E) would be expected to make a cell relatively resistant to growth inhibitory efforts of mTOR inhibition.28 The frequency of basal overexpression of eIF4E in RCC remains to be investigated. Although the groups of patients deriving clinical benefit from mTOR inhibitors and VEGF-targeted therapies appear to overlap, ideally these molecular and pathologic features can be incorporated into a selection scheme to direct the use of mTOR inhibitors in first-line, sequential, and combinational therapy for patients with RCC.

Antiangiogenic (VEGF Pathway-Targeted) Therapy

Clinical Prognostic Variables

Recent studies have addressed the issue of clinical variables that predict outcome in the setting of VEGF-targeted therapy as opposed to previous models focused on IFN treated patients.1 Patient baseline characteristics, Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1), time from diagnosis to treatment (≥1 year vs <1 year), and corrected calcium level (≤10 vs >10 mg/dL) were found to be independent pretherapy features associated with PFS in patients receiving front-line sunitinib therapy.29 Choueiri et al30 reported on the outcome of 120 patients with metastatic RCC treated with sorafenib, sunitinib, bevacizumab, and axitinib. The authors identified 5 independent poor prognostic factors by multivariable analysis: time from diagnosis to current treatment less than 2 years, corrected serum calcium level less than 8.5 mg/dL or greater than 10 mg/dL, ECOG PS higher than 0, and baseline platelet and neutrophil counts greater than 300 K/μL and greater than 4.5 K/μL, respectively. From these factors, 3 prognostic subgroups were identified with

a median PFS of 20.1 months, 13 months, and 3.9 months, respectively.30 Both prognostic models need external validation before they can be routinely adapted into clinical practice.

Biologic and Molecular Biomarkers Associated With Outcome in Advanced RCC

The TARGETs and the AVOREN phase 3 trials addressed the value of serum VEGF levels in patients who received sorafenib or the combination of bevacizumab and IFN alfa, respectively.31,32 Although high baseline VEGF levels have been associated with poor outcome, in both trials, patients with high and low baseline VEGF levels benefited from sorafenib and bevacizumab in term of PFS. This suggests that serum VEGF, while having prognostic significance, is not a predictive biomarker for benefit from VEGF-targeted therapy. A recently reported biomarker analysis from a phase 2 sunitinib trial in cytokine-refractory disease found significantly larger changes in VEGF, sVEGFR-2, and sVEGFR-3 (expressed mainly on lymphatic endothelial cells) levels at day 28 in patients exhibiting a response compared with stable disease or disease progression.33,34 Similarly, data from the a trial of pazopanib, another potent VEGFR inhibitor, showed that a more profound sVEGFR-2 level decrease at day 14 of therapy predicted a better outcome in terms of response and PFS.35 Finally, Rini et al suggested that lower baseline levels of sVEGFR-3 and VEGF-C were associated with longer PFS and better tumor response in patients receiving sunitinib following disease progression of bevacizumab.36 Whether these tests can be used to distinguish early in treatment those patients most likely to be resistant to VEGF inhibitor therapy deserves further study.

HIF Levels

Recently, Klatte et al37 showed that HIF-1α expression is an independent prognostic factor for patients with metastatic clear cell RCC. Patients with tumors exhibiting high HIF-1α expression (>35% by immunohistochemical analysis) had significantly worse survival than patients with low expression (≤35%), with a median survival of 13.5 vs 24.4 months ($P = .005$). Additionally, Patel et al38 reported on the predictive value of HIF expression in pretreatment tumor specimens by Western analysis in a small cohort of 43 patients with clear cell RCC treated with sunitinib. Interestingly, 12 (92%) of 13 patients with tumors that exhibited high HIF-2α expression (defined as >50% level relative to cell line control) responded to sunitinib compared with 4 (27%) of 15 patients whose tumors had low expression (10%-50% level) and 2 (13%) of 15 patients with tumors showing no expression (<10% level) ($P < .0001$). Additional studies are needed to confirm the predictive value of HIF-2 for sunitinib and other VEGF-targeted agents in patients with metastatic RCC.

VHL *Gene Status*

In view of the crucial role of *VHL* gene inactivation in RCC tumor biology, Choueiri et al39 reported on the *VHL* status of 123 patients with metastatic clear cell RCC with who received VEGF-targeted agents. Patients with *VHL* inactivation (*VHL* mutated or methylated) had a response rate of 41% compared with 31% for patients with a wild-type *VHL* ($P = .34$). On subgroup analysis, the presence of “loss of function” mutations (defined as frameshift, nonsense, splice, and in-frame deletions or insertions) was an independent prognostic factor associated with improved response ($P = .03$). Another interesting finding is that patients who were treated with sorafenib and bevacizumab responded only if their *VHL* gene status was inactivated in contrast to patients treated with sunitinib or axitinib who experienced responses irrespective of their *VHL* gene status. In other studies, *VHL* status did not appear to be predictive of response to axitinib (N = 13)40 or pazopanib (N = 78).35 Although data concerning the impact of VHL gene status on PFS and OS in patients receiving VEGF-targeted therapy may be more clinically relevant, these results are nonetheless of potential therapeutic significance. They suggest that either sunitinib, axitinib, and possibly pazopanib have additional non-*VHL*-related antitumor effects in RCC or that the *VHL*/HIF/VEGF

pathway remains an important target in *VHL* wild-type RCC but requires more potent inhibition for clinical activity to be manifest.

Conclusion

Investigations into the treatment selection factors for patients with advanced RCC is a work in progress. Although some information is currently available, considerably more research is needed to identify and validate selection factors for particular treatment approaches (Table 2). In the future, these approaches are likely to include not only clinical features and blood and tissue-based biomarkers but also sophisticated functional imaging studies. Such studies, including CAIX imaging for immunotherapy, positron emission imaging for TOR inhibitors, and perfusion imaging for antiangiogenic therapy, provide the potentially useful ability to noninvasively examine the metastatic lesions that are the targets of systemic therapy. Because identification of the optimal first-line treatment for a particular patient is a prerequisite to determining the optimal second-line therapy or treatment sequence, initial treatment selection research remains a priority.

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Table 1

New Standards for Clear Cell RCC Therapy

Setting	Phase 3	Alternative
First-line therapy		
Good or intermediate risk[b]	Sunitinib or bevacizumab plus interferon	High-dose IL-2
Poor risk[b]	Temsirolimus	Sunitinib
Second-line therapy		
Prior cytokine	Sorafenib	Sunitinib or bevacizumab
Prior VEGFR inhibitor	RAD001	Clinical trials
Prior mTOR inhibitor	Clinical trials	Clinical trials

Abbreviations: IL-2, interleukin 2; VEGFR, vascular endothelial growth factor receptor.

[b] Memorial Sloan-Kettering Cancer Center risk status.

Table 2

Summary of Selection Issues[a]

Treatment	Response Predictor
IL-2	CA9, histology, expression factors
Temsirolimus	Non-clear cell, high phospho-AKT, phospho-S6, PET uptake
Sorafenib	High CAIX, *VHL*-/-, high baseline perfusion
Sunitinib	High HIF-2α, *VHL*-WT

Abbreviations: CAIX, carbonic anhydrase IX; HIF, hypoxia inducible factor; IL-2, interleukin 2; PET, positron emission tomography; WT, wild type.

[a]This is a work in progress. Distinct groups of patients can likely be identified who respond best to specific therapies. More research, including prospective validation studies, is needed.