

Innovations and Challenges in Renal Cell Carcinoma: Summary Statement from the Second Cambridge Conference

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Abstract Innovations and Challenges in Renal Cancer, chaired by Michael B. Atkins, was held April 28 to 29, 2006 in Cambridge, Massachusetts. The conference brought together leading experts in the fields of cancer research, medical oncology, urology, immunology, radiology, and immunotherapy, with the goal of advancing the field of renal cancer treatment by critiquing new data from ongoing clinical trials and stimulating communication among those involved in basic and clinical research. The conference proceedings published in this educational supplement to *Clinical Cancer Research* are intended to provide timely information and recommendations on important aspects of renal cancer genetics and biology and advances in prognostic classification and treatment.

In 2006, an estimated 39,000 Americans will be diagnosed with renal cell carcinoma (RCC) and ~12,800 will die of the disease (1). RCC is now known to be composed of multiple cancer types—clear cell, papillary, chromophobe, and collecting duct—each with their distinct phenotypic appearance and molecular characteristics. Consequently, each will likely require a different treatment strategy. As more information about the biology of RCC has emerged, the therapeutic options for patients with this disease have vastly expanded. In particular, several systemic treatment options are now available for patients with metastatic clear cell RCC, the most frequent subtype. Considerable additional research is needed to determine optimally how, when, and in whom to use the various treatment approaches.

Genetics and Molecular Biology

Investigation of the inherited forms of renal cancer, including von Hippel-Lindau (VHL) disease, hereditary papillary renal

carcinoma, Birt Hogg Dubé disease, and hereditary leiomyomatosis renal cell cancer, has provided information about the etiology of various forms of sporadic RCC. The identification of similar somatic mutations in sporadic RCC has provided an opportunity to evaluate novel agents that target the downstream pathways associated with these genetic alterations, including VHL, c-Met, Birt Hogg Dubé, and fumarate hydratase (2). The most significant progress has been made in the area of agents that target the VHL/hypoxia-inducible factor (HIF)/vascular endothelial growth factor (VEGF) pathway, which is abnormal in most patients with sporadic clear cell RCC. Preclinical studies have shown that up-regulation of HIF-2 α plays a vital role in clear cell renal cancer development, which provided a rationale for exploring therapeutic agents that inhibit HIF inducible proteins such as VEGF and platelet-derived growth factor. In addition, knowledge about the VHL pathway has shown the potential to assist in diagnosis and disease subtyping and provided leads for the development of prognostic and predictive biomarkers.

The phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (mTOR) pathway has also been shown to be important in some renal tumors. Epigenetic silencing of the tumor suppressor *PTEN* occurs in approximately one third of renal cancers and leads to activation of AKT and mTOR. Activation of mTOR, in turn, promotes pathways critical to cell proliferation, cell division, and angiogenesis, the latter through stabilization of HIF, and has generally been associated with more aggressive disease. Figure 1 displays the key pathways that are abnormal in the majority of clear cell RCC and the sites of action of some of the most actively investigated targeted therapeutics.

Prognosis

Accurate prognostic information is essential for clinical management of patients with RCC, stratification for phase 3

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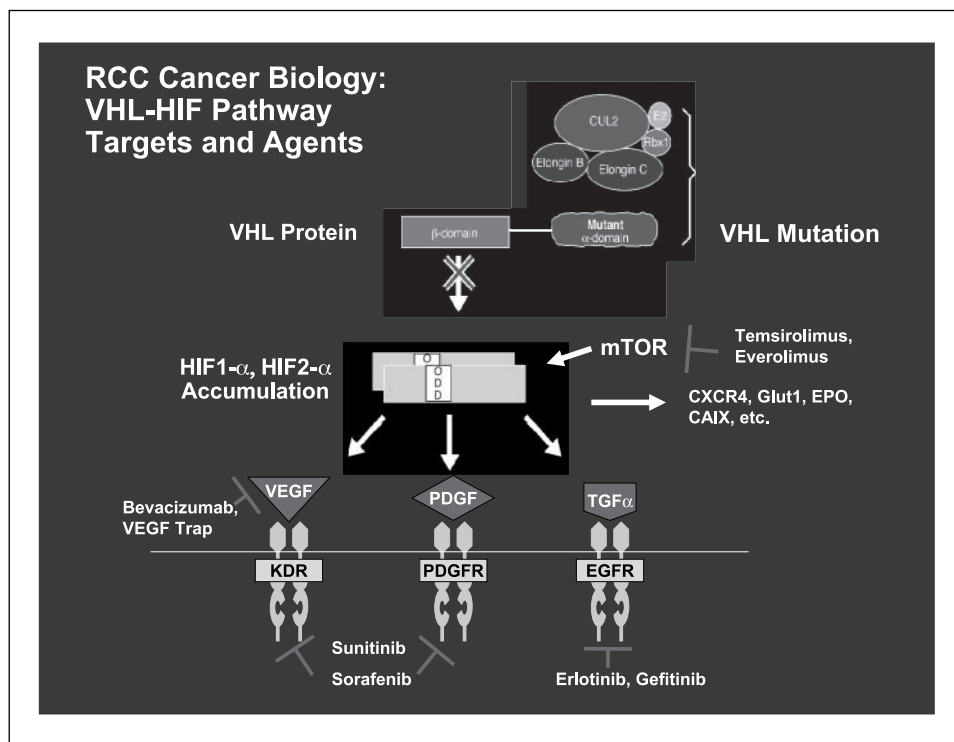


Fig. 1. Molecular biology of clear cell renal cancer. Mutations in *VHL* lead to disruption of the VHL complex, resulting in HIF accumulation even in normoxic conditions and increased expression of HIF inducible proteins including VEGF stimulating angiogenesis, platelet-derived growth factor (PDGF) promoting pericyte stabilization, and transforming growth factor- α (TGF- α) stimulating autocrine tumor growth. In addition, a number of tumors exhibit activation of mTOR via loss of suppression of the phosphatidylinositol 3-kinase-AKT pathway leading to enhanced cell proliferation and division and HIF stabilization. A number of the new targeted and antiangiogenic agents, including bevacizumab, sorafenib, sunitinib, and temsirolimus, inhibit various components of this pathway, resulting in favorable clinical results. CAIX, carbonic anhydrase IX; CUL2, Cullin 2; CXCR4, C-X-C chemokine receptor type 4; EGFR, epidermal growth factor receptor; EPO, erythropoietin; Glut1, glucose transporter 1; KDR, kinase insert domain receptor; Rbx1, Ring box protein 1.

clinical trials, and interpretation of results of some phase 2 trials. Until recently, such prognostication relied mainly on standard clinical and pathologic measures, such as tumor-node-metastasis stage, histologic grade, and performance status. Recent molecular characterization has identified other prognostic factors, such as carbonic anhydrase IX and PTEN, that can contribute to or possibly even replace the more traditional prognostic factors. In addition, tumor expression of molecules such as B7H1, which can inactivate local immune cells, has also been shown to be a powerful predictor of poor prognosis. Such prognostic markers have guided the way to novel potential therapeutic approaches for this disease, such as targeting the phosphatidylinositol 3-kinase-AKT-mTOR pathway that is activated by PTEN loss or blocking B7H1 in association with immunotherapy. In the future, both prognostic assessment and treatment choices will likely be increasingly dictated by assessments of these and similar molecules.

Adjuvant Therapy

Currently, effective adjuvant therapy for RCC patients at high risk of relapse after surgical resection does not exist. Radiation, chemotherapy, hormonal therapy, vaccines, and immunotherapy have all been tested without benefit in adjuvant setting. In particular, therapies such as IFN- α and interleukin-2 (IL-2), which have shown some benefit in patients with advanced disease, do not seem to confer significant benefit when administered as adjuvant therapies to patients after surgical resection. Adjuvant studies involving antibodies and vaccines are ongoing, whereas those involving antiangiogenic and molecularly targeted therapies have only recently been initiated, with results unlikely to be available for several years.

Immunotherapy

Vaccines. Therapeutic cancer vaccines have little proven effect in the area of RCC. Vaccine approaches have included isolated tumor cell suspensions either alone or mixed with heat shock protein, gene-modified tumor cells, and dendritic cells that express RCC-associated antigens. These cancer vaccines have reported response rates ranging from 1.9% to 9.5% (3). However, recent insights into the tumor-derived factors that inhibit the immune system have provided new opportunities to enhance vaccine-mediated antitumor immunity and thereby potentially increase vaccine efficacy. Future vaccine investigations will likely incorporate concomitant modulation of proinflammatory and immune inhibitory pathways that have hindered generation of tumor-specific immunity. Promising approaches include the combination of vaccines with antibodies to B7 molecules or agents that deplete CD25⁺ T-regulatory cells or block the generation of arginase-expressing tumor-associated myeloid cells. In addition, combinations of dendritic cell vaccines with cytokines, such as IL-2, IFN, or granulocyte-macrophage colony-stimulating factor, might produce more clinical benefit in patients with RCC.

IFN- α and IL-2. Cytokine immunotherapy has been a historical standard in metastatic RCC. IFN- α has shown a modest survival advantage in some phase III trials and in a meta-analysis, but has not fared well when directly compared with the newer antiangiogenic and molecularly targeted agents. Consequently, in the future, IFN use will likely be limited to combinations involving other active agents.

In 1992, high-dose IL-2 was approved by the Food and Drug Administration for the treatment of RCC. This agent was found to produce durable remissions in a small number of patients but was associated with considerable toxic effects. Attempts to

reduce the toxicity of IL-2 through lowering of the dose either alone or in combination with IFN- α -2b resulted in reduced response rates and significantly fewer complete and durable responses. Although high-dose IL-2 remains a standard first-line therapy for patients with metastatic RCC and is the only agent capable of producing durable complete responses, future work is needed to properly identify before treatment those patients most likely to benefit from this therapy. In addition, opportunities exist for combining IL-2-based therapy with antiangiogenic therapy, possibly producing additive or synergistic effects. These efforts are essential if IL-2 is to continue to be a major treatment option for patients with advanced RCC.

Antiangiogenic and Molecularly Targeted Therapy

Several agents that inhibit either the HIF-VEGF pathway or the effects of activated mTOR have recently shown considerable promise in patients with advanced renal cancer. The most prominent of these agents include the VEGF binding antibody, bevacizumab, the VEGF receptor tyrosine kinase inhibitors sunitinib and sorafenib, and the mTOR blockers temsirolimus and everolimus (see Fig. 1).

Bevacizumab. Bevacizumab is a ligand-binding antibody that inhibits the biological activity of VEGF. The agent was approved by the Food and Drug Administration in 2004 as a first-line treatment for patients with metastatic colorectal cancer. Bevacizumab was initially investigated in patients with metastatic RCC in a randomized phase 2 trial and found to produce tumor shrinkage in most patients and to delay median progression-free survival relative to patients receiving placebo. Treatment was generally well tolerated, with hypertension and proteinuria reported as the major associated adverse effects. Because of its excellent tolerability and established clinical activity, bevacizumab is being investigated in combination with immunotherapies such as IFN- α and IL-2 and targeted therapies such as erlotinib, sorafenib, sunitinib, and temsirolimus. Results of these trials should help to more accurately establish the potential of bevacizumab therapy and VEGF-binding strategies, in general, in patients with RCC.

Sunitinib and sorafenib. Sunitinib and sorafenib both recently received Food and Drug Administration approval for the treatment of patients with advanced RCC. Both agents have proven activity against several receptor tyrosine kinases, including VEGF receptor 2, platelet-derived growth factor receptor, c-KIT, and FLT-3. A phase 3 trial of sorafenib in cytokine refractory patients (TARGETs trial) showed a significant difference in progression-free survival compared with placebo (5.5 versus 2.8 months; $P < 0.001$; ref. 4). When progression-free survival data became available, the placebo arm of this trial was stopped and placebo-treated patients were allowed to cross over to sorafenib. Sunitinib produced objective responses in $\geq 40\%$ of patients treated in two separate multicenter phase 2 studies (5, 6). In addition, a recently reported phase III trial in largely good- and intermediate-prognosis, therapy-naïve patients with advanced RCC showed significant improvement in both response rate and progression-free survival for sunitinib relative to IFN- α (7). Although both agents are orally administered and generally well tolerated, many patients experience hypertension, skin rash, stomatitis, diarrhea, fatigue, and hand-foot syndrome, which require aggressive management and/or dose modification. Conse-

quently, it must be noted that whereas both agents have proven efficacy in treating RCC and are clearly having a major effect on progression-free survival, their effect on quality of life and overall survival has yet to be firmly established. In addition, questions about the relative potency of these two agents, their activity as adjuvant therapy, their ability to be combined with immunotherapy or other targeted therapies, their activity in patients with non-clear cell histology, and mechanisms of resistance remain to be addressed.

Temsirolimus and everolimus. Temsirolimus and everolimus are mTOR inhibitors with proven efficacy in early-stage trials in patients with advanced RCC. Everolimus has recently completed a phase 1 trial and is now being further explored both as a single agent and in combination with other targeted agents (8). A randomized phase 2 trial of temsirolimus showed antitumor activity and encouraging progression-free and overall survival rates (9). The results of a randomized three-arm phase 3 trial comparing temsirolimus with either IFN- α alone or the combination of temsirolimus and IFN- α as frontline therapy for patients with renal cancer and at least three adverse prognostic features have recently been reported (10). Single-agent temsirolimus significantly increased overall survival in this patient population relative to IFN alone, whereas the combination of lower doses of temsirolimus and IFN failed to produce a significant benefit. These results have prompted a more extensive investigation of temsirolimus and everolimus alone and in combination with other therapies both in better-prognosis first-line and sunitinib and sorafenib refractory patients. These studies will help determine the full potential of mTOR inhibitors in patients with advanced renal cancer, and hopefully will provide information on which patients are most likely to benefit from this targeted approach.

Combination therapy. Although bevacizumab, sunitinib, sorafenib, and temsirolimus have added greatly to the therapeutic armamentarium for patients with advanced renal cancer, as single agents, they do not produce complete responses, require long-term administration for continued disease control, and have several nagging adverse effects. Furthermore, treatment resistance typically develops within 6 to 12 months, and tumors often will progress quickly once treatment is stopped. Combination therapy has been proposed as a way of overcoming many of these obstacles and potentially producing more durable benefit. Although critically important, testing of combination regimens must proceed cautiously due to the potential for synergistic toxicity and/or countervailing activity inherent with these multitargeted agents. Approaches to combination therapy currently being investigated include combinations of VEGF inhibitors with immunotherapy, "vertical" combinations in which the HIF/VEGF pathway is blocked at several steps, and "horizontal" combinations in which multiple separate signaling pathways are blocked simultaneously. Efforts to understand the mechanisms underlying resistance to sunitinib and sorafenib may provide an important clue to other pathways that, if targeted in combination with these agents, could enhance and extend their clinical benefit.

Where Do We Go from Here?

With a plethora of pharmaceutical agents that have proven, although limited, efficacy in treating RCC, the question becomes, "Where do we go in terms of future drug development?"

One approach, which has been applied to other diseases, is to perform "window-of-opportunity" trials in good-prognosis, asymptomatic patients who would unlikely be harmed by the delay in standard therapy. Data from the randomized component of the randomized discontinuation phase 2 and the placebo-controlled phase 3 TARGETs trials, which show that patients crossing over to sorafenib from placebo either at progression or after some delay achieve similar benefit to those receiving sorafenib upfront, support the notion that such a patient population exists. Such trials would be able to evaluate promising novel immunotherapies or various combination regimens that might offer the possibility of producing durable benefit to a larger number of patients. Patients would need to be monitored closely for disease progression so as not to delay standard therapy longer than was necessary. In addition, it would be useful to track how such patients do with subsequent standard therapy to ensure that their overall outcome was not significantly compromised by their participation in such a clinical trial.

Conclusion

Metastatic RCC has witnessed an explosion of new potential systemic therapeutic options. As such, there are many standards of initial care in this disease. High-dose IL-2 remains the only approach to produce durable complete responses and can thus be considered in appropriately selected patients with consideration of the risk/benefit profile. Additional molecular and pathologic selection opportunities exist for cytokines, but considerable validation work is needed before these selection features can be used clinically. The role of IFN- α is less certain; however, due to its familiarity and many diverse mechanisms of action, it remains an important agent to consider in combination with other active agents. Whenever possible, cytokine therapy should be given in the context of a clinical trial investigating combination therapy and/or patient selection to maximize the benefit of this approach.

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Based on currently available data with antiangiogenic and molecularly targeted therapies, sunitinib will likely be recommended for first-line treatment of low- and intermediate-prognosis patients and temsirolimus for patients with multiple adverse prognostic features. Sorafenib remains an acceptable alternative based on the results of the TARGETs trials, although the activity of sorafenib in previously untreated patients relative to IFN has yet to be established. Little information is currently available about when to institute such treatments and which agent to choose for a particular patient. Until more information on the relative activity and biomarkers predictive of response for these various agents is available, such decisions will likely be based on clinical grounds. For example, the higher objective response rates with sunitinib may make it more suitable for patients with bulky, symptomatic disease when a significant reduction in tumor volume is of immediate importance. Alternatively, asymptomatic patients or those with certain comorbidities may be better suited to receive potentially less toxic agents such as bevacizumab or sorafenib. Finally, patients with rapidly progressive disease with many paraneoplastic symptoms might be best treated with temsirolimus. The empirical nature of these choices highlights the importance of efforts to identify patient selection criteria incorporating both clinical and molecular features (e.g., *VHL* status, pS6, carbonic anhydrase IX) to guide the use of these agents.

Recent progress in the treatment of patients with advanced renal cancer has been impressive, undeniable, and exhilarating. There are now three potentially distinct therapeutic approaches (targets): VEGF^{+/−} platelet-derived growth factor, mTOR, and immunotherapy. However, there is still considerable room for additional improvement. Any one approach is not sufficiently active to suggest that the other approaches should be abandoned. Recognizing this, we strongly support the continued exploration of molecular pathways and prognostic and predictive markers in this disease and the development of novel agents and novel treatment combinations through well-controlled, rationally designed clinical trials.