

## Innovations and Challenges in Renal Cancer: Consensus Statement from the First International Conference

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### INTRODUCTION

Innovations and Challenges in Renal Cancer, chaired by Michael B. Atkins, was held March 19 to 20, 2004, in Cambridge, MA. The conference brought together leading experts in the fields of cancer research, medical oncology, urology, and radiology who wished to exchange information and perspectives regarding recent advances and recommendations for further research in renal cell carcinoma. The conference proceedings will be of interest to oncology specialists and other health care professionals who wish to expand their knowledge of current challenges and innovations in the diagnosis and treatment of renal cell carcinoma.

The conference format combined brief scientific reports with extended periods of discussion. Throughout the confer-

ence, Michael B. Atkins asked the participants to highlight key points of their presentations that addressed the following topics: (1) important aspects of renal cell carcinoma genetics and biology, especially as they relate to early detection and therapy; (2) recent advances in prognostic classification of renal cell carcinoma, especially as these might relate to treatment selection; (3) the roles of local therapy, immunotherapy, antiangiogenic therapy, and molecularly targeted agents in the current treatment of renal cell carcinoma; and (4) recent advances in supportive care.

### RENAL CANCER GENETICS AND BIOLOGY

Renal cell carcinoma is not a single disease but rather a collection of different neoplasms, each with a distinct histologic type, natural history, and response to therapy (1). Various genetic alternations characterize these cancers, their biological phenotypes, and possible therapeutic strategies.

The best-studied form of inherited renal cell carcinoma is that associated with von Hippel-Lindau (VHL) syndrome. VHL syndrome is an autosomal dominant disease in which inheritance of one copy of a mutated allele leads to development of various cancers, including renal cell carcinoma, when a second somatic gene alteration occurs in the remaining allele. Genetic linkage analysis performed in VHL kindreds (2) resulted in the identification of the *VHL* gene on chromosome 3 in 1993 (3).

During the past decade, the biology associated with the *VHL* gene product (*pVHL*) has been elucidated, leading to promising new therapeutic targets (4). *pVHL* forms a complex with other proteins that binds to the  $\alpha$ -subunit of hypoxia-inducible factors (HIF-1 $\alpha$  and HIF-2 $\alpha$ ), resulting in polyubiquitination and subsequent proteasome-dependent degradation. HIF binding and degradation occur under normoxic conditions, when HIF is hydroxylated at specific proline residues. However, HIF hydroxylation is oxygen dependent so that under hypoxic conditions these residues remain unmodified and do not bind to the *pVHL* complex. Consequently, HIF accumulates and binds to HIF- $\beta$  in the nucleus, resulting in increased transcription of a variety of genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor B chain, and transforming growth factor  $\alpha$ . *VHL* mutations lead to a pseudohypoxic state in which the *pVHL* complex does not form or cannot target and degrade HIF, and HIF overaccumulates, even under normoxic conditions.

Loss of *VHL* and overproduction of the HIF-inducible growth factors are thought to contribute to renal cell carcinoma development. Nude mouse xenograft assays demonstrate that inhibition of HIF by *pVHL* is necessary and sufficient for tumor suppression (5, 6) and that the malignant potential of a tumor can be restored with reinsertion of HIF-2 $\alpha$ . These findings provide a rationale for treating VHL-/- renal cell carcinoma with inhibitors of HIF or its downstream targets.

A number of agents have been reported to indirectly down-regulate HIF, including rapamycin; geldenamycin; 17-

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allylamino,17-demethoxygeldanamycin; histone deacetylase inhibitors; topoisomerase I inhibitors; thioredoxin 1 inhibitors; and microtubule disruptors. Other agents, alone or in combination, that target HIF-responsive gene products are also being studied, including bevacizumab, PTK 787, SU 11248, and BAY 43-9006 (all of which inhibit VEGF or its receptors). In time, agents that target HIF-responsive angiogenic pathways might be combined with drugs that target HIF-responsive autocrine growth factors and their receptors, such as transforming growth factor  $\alpha$  and epidermal growth factor receptor.

In 1994, a previously undetected type of hereditary kidney cancer, hereditary papillary renal carcinoma, was reported (7). Affected individuals in hereditary papillary renal carcinoma kindreds were found to be at risk for the development of bilateral, multifocal type 1 papillary renal cell carcinoma. Genetic studies in hereditary papillary renal carcinoma kindreds led to the identification of the *c-Met* gene on chromosome 7 as the gene responsible for hereditary papillary renal carcinoma (8). Studies of the activating point mutations in *c-Met* found in type 1 papillary renal cell carcinoma suggest a causative role in disease progression.

Most recently, two additional familial syndromes have been linked to renal cell carcinoma: Birt-Hogg-Dubé (BHD) and fumarate hydratase (FH). BHD is a hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous nodules, pulmonary cysts and spontaneous pneumothorax, and bilateral, multifocal renal tumors (9). Genetic studies in BHD kindreds led to the localization and subsequent identification of the *BHD* gene, which appears to have the characteristics of a tumor suppressor gene (10, 11). Studies are currently under way to determine how damage to this gene leads to chromophobe renal cell carcinoma, and c-Kit has been identified as a potential therapeutic target for this disease (12). *FH*, on the other hand, has been identified as the gene for hereditary leiomyomatosis renal cell carcinoma. *FH* appears to function as a tumor suppressor gene. As with *BHD*, studies are currently examining how damage to *FH* leads to the development of type 2 papillary renal cell carcinoma.

Whereas understanding the pathways of the genes that cause renal cell carcinoma can help in the development of disease-specific therapy, uncovering molecular signatures of renal cell carcinoma (biomarkers) might help physicians identify patients with early stage disease. Genomic and proteomic analyses of human renal cell carcinoma cell lines, tumor samples, and biological fluids, such as plasma and urine, obtained from patients with renal cell carcinoma are likely to identify candidate markers. Additional prospective testing of candidate biomarkers in independent patient populations is required for marker validation. Once validated, such biomarkers could do the following: (1) serve as surrogate endpoints for preliminary studies of treatment efficacy, (2) guide additional imaging investigation to detect minimal residual disease, and (3) guide early chemotherapeutic and chemopreventive intervention.

## STAGING, PROGNOSIS, AND PREDICTORS OF RESPONSE

Identification of a reliable set of prognostic factors in patients with metastatic disease would allow investigators to

optimize patient selection for specific treatment strategies. Such prognostic factors could also assist in the interpretation of clinical trials by providing information on how therapy affects the natural history of the disease. Predictive models based on pretreatment clinical and laboratory variables can help define patients more likely to benefit from standard therapies. A few such models have been developed, but investigations into new prognostic and predictive factors based on tumor biology are needed.

Historically, clinical factors alone were used as prognostic markers for patients with renal cell carcinoma. The first report that addressed the use of clinical variables as prognostic markers appeared in 1986 (13). The authors of this study identified the following factors as predictive of patient outcome: performance status, the presence of pulmonary metastases, and the metastatic-free interval. In 1999, the Memorial Sloan-Kettering Cancer Center published a study on the relationship between pretreatment clinical features and survival in patients treated in Phase II and III clinical trials for metastatic renal cell carcinoma (14). The Memorial Sloan-Kettering Cancer Center study used five prognostic factors: performance status, lactate dehydrogenase level, hemoglobin level, corrected serum calcium level, and nephrectomy status. The study showed that these prognostic factors could be used to categorize patients into good, intermediate, and poor risk groups. The Memorial Sloan-Kettering Cancer Center model was validated by a study from The Cleveland Clinic Foundation.<sup>18</sup> As a result of these studies, a group of international investigators (International Kidney Cancer Working Group) is currently creating a comprehensive database of >4,000 patients with metastatic renal cell carcinoma to provide and validate a single model that can be used to predict survival.

Although prognostic models for renal cell carcinoma based on clinical variables alone have proven useful, biomarkers for disease prognosis might offer better insight into the molecular mechanisms of disease progression. Gene expression and tissue microarray analyses permit rapid molecular and protein expression profiling of tissue specimens, providing potential expression patterns that can be associated with clinical outcome and underlying tumor biology. Studies based on gene expression arrays, which screen for differential expression of thousands of genes, have identified large numbers of new, potentially important prognostic markers (15). Currently, markers relating to tumor proliferation, tumor growth, angiogenesis, and loss of cell adhesion are being evaluated for their potential as prognostic factors. Studies based on tissue microarrays have revealed that CA-IX is highly expressed in renal cell carcinoma and may be a useful prognostic and predictive marker for this disease (16). The development of staging systems based on gene expression and tissue microarrays may prove to be a powerful tool for evaluating tumors simultaneously with histologic, immunohistochemical, and chromosomal analyses.

<sup>18</sup> T. M. Mekhail, R. A. Gawda, G. Abou Mari, et al. Validation and extension of the Memorial Sloan Kettering Prognostic Factor Model for survival in patients with previously untreated metastatic renal cell carcinoma, manuscript in preparation.

## LOCAL-REGIONAL THERAPY

Radical nephrectomy continues to be the gold standard for treating patients with localized renal cell carcinoma. However, a better understanding of the biology of renal cell carcinoma, standardized staging of the disease, and changing patterns of patient presentation permit a refined management approach that may include nephron-sparing surgery (17). The use of nephron-sparing surgery has been established in patients with localized renal cell carcinoma when there is a clinically relevant need to preserve renal function. It is also indicated in patients with single, small, unilateral, localized renal cell carcinoma when the opposite kidney is completely normal. Open surgical partial nephrectomy remains the established standard for nephron-sparing treatment of renal tumors. When applied to small renal tumors, the laparoscopic approach is associated with longer warm renal ischemia time, more major intraoperative complications, and more postoperative urologic complications. Nevertheless, data suggest that laparoscopic nephron-sparing surgery is emerging as an effective, minimally invasive therapeutic approach with respect to renal functional outcome, with additional advantages of reduced postoperative narcotic use, earlier hospital discharge, and faster convalescence. Continued efforts are required to develop laparoscopic renal hypothermia techniques and to facilitate intrarenal suturing while minimizing the warm ischemia time.

The use of nephrectomy in patients with metastatic renal cell carcinoma has become an accepted standard for selected groups of patients. Nephrectomy for palliation of symptoms related to the primary tumor or metastases is justified in the rare patient whose symptoms cannot adequately be controlled by other strategies. Resection of the primary tumor and solitary or limited metastases can sometimes lead to long-term survival, but few patients satisfy the criteria for this type of surgery. Cytokine-based immunotherapy is considered the standard treatment for patients with metastatic renal cell carcinoma. For patients presenting with advanced renal cell carcinoma, preimmunotherapy cytoreductive nephrectomy has been shown to result in a modest survival benefit for patients with good performance status and limited burden of metastatic disease (18). Whether cytoreductive nephrectomy before molecularly targeted or antiangiogenic therapy will produce similar survival benefit remains to be seen. In addition, the value of pretreatment nephrectomy in patients presenting with significant and/or symptomatic distant metastases remains to be established.

Another tool in the armamentarium of renal cell carcinoma therapy is radiofrequency ablation. Radiofrequency ablation has been used to treat focal liver tumors, but more recently this technique has been applied to focal renal tumors. Potential benefits of radiofrequency ablation include reduced morbidity and mortality compared with standard surgical resection and the ability to treat nonsurgical patients. Tumor size and location are the two most important factors that govern whether renal cell carcinoma can be successfully treated. Radiofrequency ablation cannot yet reliably treat tumors >5 cm or centrally located tumors. Future clinical studies are needed to determine local recurrence, complication, and long-term survival rates for this procedure.

## IMMUNOTHERAPY

Immunoreactive cytokines have been the mainstay of treatment of renal cell carcinoma for the past 15 years. Most research has focused on interleukin 2 (IL-2) and interferon  $\alpha$ . However, neither agent has proved sufficient for treating renal cell carcinoma patients. Interferon has been studied in a variety of preparations, doses, and schedules, but most studies have shown the agent to have modest antitumor activity, with overall response rates ranging from ~10% to 15% and a 2- to 3-month prolongation in median survival (19). In addition, most responses with interferon are delayed, partial, and short-lived (19). Despite these drawbacks, interferon continues to be actively investigated in patients with advanced renal cell carcinoma. Its excellent safety profile, multiple potential mechanisms of action, outpatient administration schedule, and familiarity to oncologists have prompted the study of its use in combination with other potentially active agents in renal cell carcinoma, including IL-2, 13-*cis*-retinoic acid, thalidomide, CCI-779, and bevacizumab. IL-2 remains the only United States Food and Drug Administration-approved treatment for advanced renal cell carcinoma. Approval was awarded in 1992 based on the documented ability of high-dose IL-2 to produce durable, high-quality tumor responses in a small but meaningful percentage of patients. Unfortunately, high-dose IL-2 also has many severe adverse effects, limiting its availability to selected patients treated at a few centers with expertise in this therapy. Recent research has identified several clinical, pathological, and even molecular parameters that appear to predict for benefit to IL-2 therapy, raising the possibility of limiting this toxic treatment to those most likely to benefit. Additional research into novel immunotherapies, such as dendritic cell (DC) vaccination and allogeneic bone marrow stem cell transplantation, may yet expand the application of immunotherapy in this disease.

One interesting area of investigation is the use of cancer vaccines to activate host immune cells to specifically target and eliminate malignant cells. A promising approach for the design of cancer vaccines involves the fusion of whole tumor cells with DCs. The DC-tumor fusion presents a spectrum of tumor-associated antigens to helper and cytotoxic T-cell populations in the context of DC-mediated costimulatory signals. In animal models, vaccination with DC-tumor fusions has resulted in protection from tumor challenge and regression of established metastatic disease. Clinical trials have been conducted in which patients with breast and renal cancer have undergone vaccination with autologous DC-tumor fusions. Therapy was well tolerated, and antitumor immunity has been observed in a subset of patients. Future studies are needed to explore the effect of DC maturation and cytokine adjuvants on vaccine potency.

Another exciting area in the field of renal cell carcinoma therapy is the use of allogeneic hematopoietic stem cell transplantation in treating patients with solid tumors. Allogeneic hematopoietic stem cell transplantation is widely accepted as a potent form of immunotherapy capable of curing patients with chemotherapy-refractory hematologic malignancies; however, within the last decade, investigators have begun exploring allogeneic transplantation as immunotherapy for epithelial malignancies. Early pilot trials have established proof of principle that graft-*versus*-tumor effects can induce complete or partial remis-

sion in some patients with treatment-refractory renal cell carcinoma (20). Second-generation allogeneic transplantation trials are now needed to incorporate methods of enhancing the donor immune system against the tumor through the use of adoptively infused tumor-reactive donor T cells, natural killer cells, and post-transplantation tumor vaccination strategies.

Additional investigations are considering other agents in the treatment of renal cell carcinoma. There is evidence that immune responses to renal cell carcinoma protect patients against progression of the disease and in some cases mediate tumor regression. Investigations are ongoing to determine whether tumor-derived products, including gangliosides isolated from renal cell carcinoma patients, participate in the down-regulation of such type 1 T-cell responses. Preliminary results have shown that inhibition of type 1 T-cell responses represents a relevant mechanism by which renal cell carcinoma can inhibit protective antitumor immunity and, thus, promote tumor survival and progression.

## TARGETED THERAPY

A greater understanding of cancer genetics has led to the development of novel therapeutic agents that are directed against growth factor targets linked to specific types of cancer. Renal cell carcinoma represents a prime target for these approaches, with the most promising results being produced with agents that inhibit VEGF.

Bevacizumab, a neutralizing antibody to VEGF, is one such targeted therapy currently being studied. A recent randomized, placebo-controlled, double-blind, Phase II trial (19) using bevacizumab showed that doses of 3 or 10 mg/kg every 2 weeks produced minimal toxic effects, with hypertension and proteinuria the most significant events. Four of 39 patients treated at the 10-mg/kg dose level achieved partial responses, and this dose also produced a highly significant prolongation of time to tumor progression. Four patients have been undergoing long-term bevacizumab therapy without tumor progression for 3 to 5 years, and of these, 3 have significant proteinuria but retain normal renal function. A small pilot trial that combined bevacizumab and thalidomide showed no unexpected toxic effects but no additional benefits. Future trials should consider combination therapies and strategies where patients are treated through initial disease progression with antiangiogenic agents such as bevacizumab. Various inhibitors of VEGF receptor signaling, including PTK 787, SU 11248, and BAY 43-9006, have also been studied in patients with renal cell carcinoma, and each of these agents shows encouraging results.

Another pathway that has been identified as a potential target for anticancer therapy is the mammalian target of rapamycin (mTOR). The mTOR pathway was first recognized in studies examining the activity of the immunosuppressive drug rapamycin. Since its identification, mTOR has emerged as a key regulator of the cell cycle and many intracellular functions, making it a potential target for antitumor therapy. mTOR activation is regulated by the PTEN-AKT system. Many patients with renal cell carcinoma have suppressed PTEN expression, leading to enhanced AKT and mTOR activity. In addition, recent data suggest the mTOR also serves to regulate HIF. Several agents targeted to mTOR are currently being investi-

gated, including CCI-779 and RAD-001. Both of these agents have entered clinical trials, and another mTOR inhibitor, ap23573, is in preclinical evaluation.

Agents targeted to the RAS-RAF-MEK-ERK-MAP kinase pathway, which is controlled by receptor tyrosine kinase activation, are also being explored. One such agent is BAY 43-9006, which blocks C-RAF signaling. In addition, this agent has also been shown to block VEGF receptor-mediated signaling. Phase II trials of this oral agent have shown tumor responses (minor response or partial response) in >30% of patients (20). A Phase III trial of BAY 43-9006 has started for patients whose renal cell carcinoma has progressed within 6 months of immunotherapy. Combination studies with interferon, IL-2, bevacizumab, and chemotherapy are under consideration.

Activation or overexpression of a particular pathway is not enough to make that pathway a good therapeutic target. The molecular abnormality has to be both necessary and sufficient for malignant growth. As such, additional development of HIF-dependent targets in patients with documented VHL-/- metastatic renal cell carcinoma is reasonable. In contrast, until our understanding of the biology of variant renal cell carcinoma improves, treatment strategies will have to be based on clinical observations. To aid in this decision making, a central registry of patients with variant renal cell carcinoma should be created in which response to various therapies is recorded. Such a registry could provide support for a more formal multi-institutional study investigating specific drugs or regimens.

## SUMMARY STATEMENT

Renal cell carcinoma is a serious medical problem in the United States, with nearly 35,000 new cases and >12,000 cancer-related deaths reported in 2003 (21). A number of exciting advances in understanding the genetics, biology, and prognostic and predictive factors for renal cell carcinoma, as well as better local therapies, are improving the outlook for patients with advanced renal cell carcinoma.

Although combinations of various treatment approaches might produce synergistic antitumor activity, we lack the mechanisms to rapidly and efficiently identify potentially effective combinations. Good surrogates of biological effect are needed to efficiently study strategies for combining various approaches. Nonetheless, for the first time in many years, investigators are primed to make significant advances in the treatment of renal cell carcinoma.

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