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Innovations and Challenges in Renal Cancer: Summary Statement From the Third Cambridge Conference

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Abstract

The Third Cambridge Conference on Innovations and Challenges in Renal Cancer, a symposium held in Cambridge, Massachusetts, June 27–28, 2008, and chaired by Michael B. Atkins, was convened to discuss the current state of knowledge in the field, critique new data, stimulate communication among those involved in basic and clinical research, and offer recommendations for further study. Four main topics were discussed: genetics and molecular biology of renal cell cancer, staging and prognosis, systemic therapy, and correlative science and biomarkers in stage IV disease. The conference format combined brief presentations with extended periods of discussion. The conclusions and recommendations are summarized in this paper and presented in more detail in the individual papers that follow.

Keywords

renal cancer; genetics; molecular biology; staging; prognosis; systemic therapy; correlative science; biomarkers

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Introduction

In 2008, an estimated 54,390 new cases of renal cell cancer (RCC) will be diagnosed in the United States and 13,010 people will die of this disease.1 Patients with organ confined disease whose cancer is detected and treated early have 5-year survival rates approaching 85%.2 However, in patients with metastatic disease and those who experience relapse after curative nephrectomy, the expected 5-year survival rate is only approximately 10%.2 Renal cancer is made up of several different types of cancer, each of which responds differently to treatment. However, 3 potentially distinct targets and related therapeutic approaches are currently available: vascular endothelial growth factor (VEGF) (antiangiogenic therapy), mTOR (targeted therapy), and immunotherapy. Additional research is urgently needed into optimal ways of using these treatment strategies, identification of new therapeutic targets, and identification of patients most likely to benefit from each particular treatment.

Genetics and Molecular Biology

Our genetic and clinical experience suggests that there is a significant opportunity to develop potential therapeutic agents that target the metabolic defects in renal cell cancers. Identification of the *MET*, *BHD*, *FH*, and *VHL* genes in renal cancer has enabled the development of targeted approaches to treat both hereditary and sporadic renal cancer. Early studies of the *MET*, *BHD*, and *FH* genes have provided a basis for potential therapies for hereditary papillary RCC, noninherited papillary RCC, BHD-associated kidney cancer, hereditary leiomyomatosis RCC-associated kidney cancer, and nonfamilial type 2 papillary kidney cancer.[3] Antiangiogenic agents, such as sorafenib, suntinib, and bevacizumab, that target the downstream effects of *VHL* loss and *HIF* upregulation have shown remarkable, albeit still less than desired, benefit in the treatment of patients with clear cell kidney cancer.[4–6] We are continuing to identify HIF dependent and independent functions of the VHL protein that contribute to kidney cancer and genes that when mutated cooperate with VHL loss to cause kidney cancer. In addition, we are trying to identify unique vulnerabilities that are created in cells that lack the VHL protein that might lend themselves to therapeutic approaches. Some of these pathways might include the PI3kinase/AKT/mTor pathway, which is the target of mTOR inhibitors such as temsirolimus and everolimus, and the c-met pathway, which may either cooperate with VHL loss or be active by itself in inducing RCC growth.[7]

Staging and Prognosis

Although many different clinical factors have been studied as potential prognostic factors in RCC, the ability of these factors to serve as independent predictors of prognosis is difficult to assess because of variations in definitions, coding, and populations studied. Gene expression profiling has revealed both VHL-HIF–related and non–VHL-HIF– related prognostic factors and differences in the vasculature between low-grade and high-grade tumors.[8] In addition, it is necessary to refine prognostic factor models using additional clinical criteria and biomarkers. Current studies are attempting to identify RCC-specific biomarkers that can improve early diagnosis, tumor progression surveillance, and prediction of patient prognosis. Yet, the development of robust tissue-based biomarkers that can be used in the clinical setting requires a standardization of various procedures involved in the process. This standardization has to be developed for all the 3 major phases of tissue biomarker studies: (1) the preanalytical phase, which includes the collection, processing, and storage of the tissue; (2) the analytical phase, during which the tissue is analyzed in the laboratory; and (3) the postanalytical phase, during which interpretation of results and data analysis are performed.

Systemic Therapy

Renal cell carcinoma evokes an immune response that can result in significant disease remission. Various immunotherapeutic strategies have been studied in an attempt to reproduce or accentuate this response. The most consistent antitumor activity has been reported with interferon alfa and interleukin 2. Previous studies have revealed that the more effective agent, in terms of response rate and quality, is high-dose intravenous bolus interleukin 2.9,[10] Future studies on the immune system are needed to help us identify predictors of response (or resistance) and to allow ready identification of patients with metastatic kidney cancer most likely to have a durable response to immunotherapy .

Currently, the most active agents for treating RCC are vascular endothelial growth factor (VEGF)–targeting antiangiogenic agents, which have been shown to significantly delay disease progression and likely extend survival of patients with kidney cancer. Studies of agents that bind circulating VEGF protein (eg, bevacizumab) and of small molecule inhibitors of the receptor to which the VEGF ligand binds (eg, sunitinib, sorafenib, axitinib, and pazopanib) have produced significant clinical effects, including high objective response rates, prolonged progression-free survival, and long overall survival times.[11–15] Future studies need to investigate combination and sequential therapy, mechanisms of response and resistance, and the effect of these agents in other disease settings.

Another potential therapy currently being explored in renal cancer is PI3K/Akt/mTOR-targeted therapy. Temsirolimus has been shown to improve overall survival in patients with advanced renal cancer and poor prognostic features compared with interferon.[16] Everolimus improves progression-free survival in patients in whom sunitinib and/or sorafenib therapy has ceased to be effective.[17] Although these findings are encouraging, the mechanisms of PI3K/Akt/mTOR-targeted therapy are incompletely understood. For example, it is unclear to what extent the therapeutic benefit is mediated by antiangiogenic effects, perhaps via diminished HIF production versus direct effects on cell proliferation mediated by mTOR inhibition. In addition, questions surround the potential impact of the loss of feedback inhibition of insulin receptor substate/PI3K signaling resulting from the inhibition of mTOR complex 1 by rapamycin analogs and the activating phosphorylation of Akt by mTOR complex 2. The modest activity of rapamycin analogs in renal cell carcinoma suggests there are additional opportunities for targeting the PI3 kinase AKT pathway, but further research is necessary.

Because of the promising results seen with the single agents discussed above, sequential therapy has become the de facto standard of care in patients with RCC. Although sequential therapy undoubtedly has contributed to the apparent improvement in median overall survival now reported in most RCC studies, little formal testing of specific sequences or strategies has taken place to date. Much work is needed to help determine the most effective sequence of drugs in select patient populations. Regarding patient selection issues, future studies are also needed to help identify which patients are most likely to respond to the currently available therapies. Such studies will most likely include not only investigation of clinical features and blood- and tissue-based biomarkers but also sophisticated functional imaging studies.

There has also been a considerable effort placed on developing combination regimens. To date, combination studies have produced mixed results. Although combinations of different treatment strategies have been reasonably well tolerated (mTOR + VEGF pathway inhibition or VEGF pathway inhibition + immunotherapy), it remains to be established whether the combination is more effective than the single agents given in sequence or even the more effective agent in the combination administered alone. Furthermore, attempts to block the VEGF pathway at multiple levels (with bevacizumab and a VEGF receptor tyrosine kinase inhibitor) have produced toxic effects, perhaps indicating that we are nearing the limit of

therapeutic benefit that can be achieved through inhibiting VEGF-mediated angiogenesis in kidney cancer.

Correlative Science and Biomarkers

Because of the strides made in developing targeted therapies for RCC, several unmet needs must be addressed to advance the science. Accurate histologic subtyping of tumors has become even more important as we attempt to determine how best to administer these therapies. Magnetic resonance imaging (MRI) provides an opportunity to accurately characterize the histologic subtype of renal cell cancer noninvasively and to provide surrogate markers associated with the biologic features of RCC. Two types of MRI techniques that have been studied for their ability to determine histologic tumor subtype and to assess tumor vascularization and perfusion are dynamic contrast– enhanced (DCE) MRI and arterial spin labeling (ASL). DCE MRI allows the identification of distinct patterns of enhancement among the different histologic subtypes[18] but is limited in clinical trials by its poor standardization across different vendors and the lack of direct quantification of tumor perfusion. ASL imaging has shown promise in its ability to accurately assess the effects of antiangiogenic therapy on tumor perfusion, but the clinical significance and general applicability of these findings needs to be established in larger studies using current therapies. 19

Additional validation is also needed in the area of blood-based biomarkers for renal cancer. Biomarkers such as circulating proangiogenic factors and receptors, markers of hypoxia and endothelial damage, and cellular populations in peripheral blood, such as circulating endothelial cells, have achieved some success in identifying which patients are most likely to respond to treatment or experience toxic effects, in aiding the selection of optimal doses, and in determining whether the intended molecular target has been effectively inhibited. Sophisticated technologies to fully understand the activity of various treatment approaches and to measure the extent of target inhibition are being developed.

Along with how and to whom these new targeted therapies should be administered is the question of when to administer therapy. Presurgical or neoadjuvant therapy is a novel approach to the treatment of metastatic and locally advanced renal cancer. Initial results suggest that it is safe and not associated with untoward morbidity or mortality, but future studies are necessary to determine the efficacy of this approach.

Future Directions

Although recent progress in the treatment of patients with advanced RCC is impressive, there is still considerable need for further advances. Combination and sequential therapies are attractive treatment approaches but still need to be pursued carefully with regard to acute and chronic toxicity and to determine their relative benefit. Treatment with the VEGF receptor antagonists appears to induce a number of alternative factors that influence growth, tumor invasiveness, and angiogenesis. It may be possible to improve the efficacy of these therapies by inhibition of these compensatory mechanisms that promote tumor survival in the setting of VEGF pathway blockade. Novel agents are also in development for the treatment of RCC, including second-generation VEGF receptor tyrosine kinase inhibitors (eg, axitinib, pazopanib), c-met inhibitors (eg, XL880), Akt inhibitors (eg, perifosine), angiopoietin/Tie-2 inhibitors (eg, AMG 386), monoclonal antibodies (VEGF-Trap), and immunostimulatory agents (CTLA4 and Trovax). However, the effective use of these novel agents requires continued understanding of the biology of renal cell carcinoma. Novel trial designs of combination, sequential, and new agents will be required to establish the impact of these approaches on patient outcome.

Conclusion

This conference provided the opportunity for leading experts in the fields of cancer research, medical oncology, urology, immunology, radiology, and immunotherapy to discuss and prioritize research topics in renal cancer. Table 1 lists the top 5 research priorities identified by the authors in order of importance. The first priority is to examine the mechanisms of acquired VEGF receptor resistance, which will most likely involve the study of key signaling pathways used by RCC cells to adjust to the loss of VEGF signaling. The second priority is to identify new targets (particularly those within the tumor) and then test inhibitors of those targets in defined patient populations in order to ensure a fair assessment. The third priority is to identify predictive and surrogate biomarkers, which will help select patients for particular therapies and provide early information on treatment efficacy. The fourth priority is to explore combination vs sequential therapy with an eye toward determining the most beneficial approach for renal cancer patients. Finally, mechanisms of response need to be explored, with a particular emphasis on how that might lead to the development of more effective agents and more rational treatment sequencing.

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Table 1

Top 5 Research Priorities in Order of Importance

Mechanisms of acquired vascular endothelial growth factor receptor resistance
New targets (particularly those within the tumor)
Predictive and surrogate biomarkers
Combination vs sequential therapy
Mechanisms of response