Kidney Cancer Research: Developing a New Vision for the Future

A symposium for young investigators, hosted by the Kidney Cancer Association, September 7, 2011

Introduction

Since the founding of the Kidney Cancer Association (KCA) just over 20 years ago, the medical community has made enormous progress in developing new strategies aimed at improving the health outcomes of patients diagnosed with kidney cancer -- and ultimately, finding a cure for the disease.

These advancements have been particularly pronounced in the last six years; a time during which the Food and Drug Administration (FDA) approved six new therapeutic options to slow the progression of kidney cancer. Surgical techniques have also improved in recent years, giving patients more options.

The dizzying pace of scientific advance has given us great optimism for the future; but it has also created an environment in which researchers find themselves contemplating just as many new questions as new answers. With so many options for treatment now, and so many new data sets to compare as we seek better understanding of the clinical impact of our new strategies, our knowledge base is more complex and fluid than ever.

Thus, in 2011 the kidney cancer research community faces fundamental questions: How can we best leverage our new-found data wealth? How can we share this data faster and more broadly in order to maximize its impact? In view of all we have learned over the last several years, what should our research priorities be? And perhaps most important of all – how can we encourage the development of a new generation of researchers, inspired to move our clinical knowledge-base to the next level?

With these questions as a backdrop, the KCA began organizing a research symposium in 2011 that would feature the input and ideas of some of today's most promising and gifted young kidney cancer researchers. Convened on September 7, 2011 in Chicago, the one-day symposium linked 16 young researchers with several prominent mid-career researchers in small-group and large-group discussions to address a set of key questions for the kidney cancer medical community.

The symposium would be the first of its kind since a similar event was held by the KCA in 1997.

Recognizing that an effective research community must be dynamically engaged and promote partnership and collaboration between innovators, a key goal of the symposium was to foster closer relationships between symposium participants and help them learn more about each other's work.

Over the course of the day, participants were asked to answer six questions intended to review what is considered "state of the art" in kidney cancer research, examine limitations and opportunities in current treatment strategies, and define the core elements needed for an effective discipline-wide research agenda.

This document provides highlights of these discussions and a framework for action as the kidney cancer research community ponders its future.

Background/Executive Summary

Kidney cancer research has yielded impressive results in recent years; still, we are far from a cure. The impact of the last decade's worth of research has been an explosion of new treatment options.

Renal Cell Carcinoma (RCC) has historically been a difficult cancer to treat, with surgery being the cornerstone of clinical options. For years, radical nephrectomy was the basic path for patients – many thousands of whom survived their cancer as a result.

Systemic therapies were limited to toxic agents Interferon and Interleukin 2.

Because treatment options were so limited, few academics focused on RCC . Pathological classification remained unsophisticated; little was known about the underlying causes of the disease.

Following an international meeting of experts on The Classification of Renal Cell Tumours, held in Heidelberg, Germany, in 1997, kidney cancer was divided into five histological types based on immunology and underlying genetics. These include:

- Conventional (or clear cell) RCC, the most common form of RCC.
- Papillary cell tumors (thought to arise from the proximal tubule).
- Chromophobe, resembling the intercalated cells type B from the cortical collecting duct.
- Renal oncocytoma (now regarded as a benign tumor, thought to arise from the distal nephron).
- Collecting duct (duct Bellini), closely related to the principal cells of the medullary collecting duct.

The categorizing progress of the 1990s was largely fostered by the use of monoclonal antibodies to characterize kidney cancer cells, as well as the recognition of the molecular genetics of each subset through the study of rare familial forms of kidney cancer.

In general, medical therapy aimed at RCC has been revolutionized by advances in the understanding of the familial Von Hippel-Lindau (VHL) Syndrome, identified in patients with a familial form of kidney cancer. A mutation of the VHL gene on chromosome 3 was found to be a major factor in clear cell carcinoma pathogenesis. The medical community's new understanding of the VHL gene and the pathogenesis of cancer has led to the development of new targeted therapies.

A second key pathway – mammalian target of rapamycin (mTOR) -- potentially regulating kidney cancer growth, was also identified in recent years. Activation of this pathway may facilitate cancer growth and progression by various mechanisms, including through stimulation of tumor-associated angiogenesis.

These breakthrough advances were precursors to the development of new drug therapies and advanced surgical techniques in recent years; virtually all targeted therapies are aimed at one or both of the major pathways (mTOR and the VHL gene.)

Six new drugs have been developed since 2005, which are now widely used as first or second line treatments against RCC: sorafenib tosylate (Nexavar), sunitinib malate (Sutent), pazopanib (Votrient), bevacizumab (Avastin), temsirolimus (Torisel), and everolimus (Afinitor).

The swift progress of the pharmaceutical industry in developing these new drugs has in turn created a new clinical environment, in which researchers are able to focus on early detection, creation of less invasive techniques and new therapies for advanced disease.

Researchers are now focusing attention on the best use of these new agents, including how to individualize treatment by determining optimal sequences of use, possible drug combinations, the predictability of outcomes, and their potential role in the adjuvant setting following nephrectomy.

The research community is also seeking to better understand why tumors become resistant to the new targeted therapies, returning to the biology of the tumors in an effort to sort out the variability of response and seeking predictability.

In general, recent advances -- and particularly those of the last six years -- have yielded three key areas of progress since the KCA's 1997 research symposium:

- Significant progress in surgical techniques and surgical management.
- Better understanding of the histological basis of RCC and its underlying biology.
- Advances in medical management and the integration of surgery into the medical management model.

About the Participants

The 16 participants in the KCA symposium were sought out for their expertise and promise in three primary categories: treatment of advanced disease, translational research and surgery. Each is a recognized emerging young leader in one or several of these categories. Several leading mid-career researchers were also selected to participate as discussion facilitators during the proceedings.

Key Questions

During the symposium, participants structured their discussions around six key questions, interacting in both large-group and small-group sessions:

- What are the five most important areas of accomplishment in kidney cancer research in the past 5 to 10 years?
- What are the major limitations of kidney cancer treatment?

- What are the unmet needs for research?
- What are the priorities of research for the next 10 years?
- What resources are needed in order to address these priorities and unmet needs?
- How can the Kidney Cancer Association, industry, the National Cancer Institute and other funding organizations best use their resources to facilitate kidney cancer research?

Symposium Summary

After a general large-group discussion of the current state of kidney cancer research and clinical practice, participants broke into three small groups of approximately five to six individuals to consider the day's key questions.

Group One: Treatment of Advanced Disease

What are the most important areas of accomplishment and the major areas of limitation in the treatment of advanced disease?

The rate of survival has significantly improved with targeted therapies; survival has doubled overall in recent years. At the same time, the quality of life has markedly improved for most patients, with fewer and less impactful side effects associated with treatments. We have begun a paradigm shift from "deadly" to "chronic"; for some patients, kidney cancer has become a condition that is manageable.

A key advance in advanced disease has been the identification of two critical therapeutic pathways: angiogenesis and mTOR

While the medical community is making great progress with therapies, however, the group noted that the goal should be "cure" – not simply "treatment."

Group One noted that research in advanced disease is becoming somewhat stagnant, having reached a high-water mark with current drugs. New drugs are needed to take treatment advances to the next level. While there are a large number of drugs, they are grouped in only three categories – cytokine, VEGF and mTOR. Drug categories must be expanded.

To reach a new level, research must move beyond the sequencing and combining of mTOR and VEGF inhibitors. A better understanding and definition of the mechanisms of resistance to VEGF and mTOR pathways is needed. The kidney cancer research community is lagging behind research into other forms of cancer in this regard (melanoma research, for example.)

Most current therapies are geared towards clear-cell Renal Cell Carcinoma (RCC), but data is lacking for non-clear-cell RCC. Similarly, there is a lopsided emphasis on "HIF-centric" molecular biology in the current treatment environment; the research community needs to move beyond this orientation to find new targets.

What are the unmet needs for advanced-treatment research and what should the priorities of research be over the next 10 years?

Group One singled out several new directions for research – among them, defining new immunotherapeutic targets, such as PD-1 and novel approaches to immunotherapy – for example, G250 radiolabeled monoclonal antibody.

Key under-addressed areas in research include rare types of kidney cancer – notably non-clear-cell RCC – and the need for research consortia. There is currently a lack of clinical trials and collaboration across research centers.

The group noted that currently, some patients do well despite therapies – a better understanding of this biologic subset is needed. Who are these patients and what can we learn about them? The group discussed the potential of predictive bio-markers as a tool in developing treatment strategies.

The group called for specifically designed therapeutic trials for non-clear cell subtypes and a better understanding of non-clear cell RCC biology, noting that multicenter collaboration will be crucial to achieve this goal.

Just as the research community needs to focus investigation on patients who do well despite therapies, it must also work to develop improved therapies for poor-risk patients – those who do poorly no matter what therapeutic path is followed. The research community should focus more closely, as well, on mechanisms of acquired resistance to mTOR and VEGF.

Group One also discussed patients who are primary refractory to VEGF, noting the lack of therapies specifically aimed at them. The group felt that more biopsy-study of these patients would be worthwhile.

The group examined a number of issues that are working to the kidney cancer research community's disadvantage at present. Among them: other disease-states (prostate cancer and myeloma, for example) have well-organized consortia to help advance research needs not met by industry and cooperative groups. Additionally, funding and liability issues can inhibit the opening of new investigator-initiated projects at medical centers.

The group discussed extensively the issue of biopsies, including costs and patient motivation. A number of questions have emerged regarding biopsies, including:

- Are biopsies the only way to access tissue for translational analysis?
- Are we getting good quality tissue?
- Can we bring the costs of biopsy down for research purposes?
- How can patient buy-in be improved?

The group also identified several key questions for the research community to confront as it seeks a new level of scientific progress, putting an emphasis on clinical trials:

- How can we better use the accumulated results of past clinical trials in order to move forward?
- How should future trials be designed?
- How can we best collaborate with industry to focus on the right agents and to design the most effective trials?
- Is the creation of a central, collaborative, annotated tissue bank achievable?
- Could a business model be developed that would better support academic clinical research?

How can the Kidney Cancer Association, industry, the National Cancer Institute and other funding organizations best use their resources to facilitate kidney cancer research?

Group One discussed the role KCA and other organizations could play in helping move a new vision for kidney cancer research forward. They noted that one of KCA's great strengths is that it acts as an information clearinghouse to link patients to available clinical trials; in a current environment in which accrual is down, KCA could increase its efforts to advocate for greater clinical-trial enrollment and better awareness of trials among patients and families.

The lack of a robust tumor registry is a significant issue for the kidney cancer research community. The group felt that industry should be urged to collect and bank tissue from large trials, linking it to clinical data. LOIs could then be proposed for those samples.

Group One also identified structural elements for new clinical trials that would help move the kidney cancer knowledgebase forward. They should:

- Have a translational component; a "value-added" proposition
- They should represent a well-defined departure from previous clinical trials
- Predictive biomarkers should be a priority

The goal is to generate a culture that fosters truly informative and original clinical research – moving in new directions, and building upon our current knowledge base. This will be accomplished via stronger partnerships between government, industry and academia. While the last several years have yielded excellent results for patients, opportunities have been lost due to the lack of a stronger research infrastructure.

<u>Group Two: Surgery</u>

What are the most important areas of accomplishment and the major areas of limitation in the surgical treatment of kidney cancer?

The last decade has been an exciting period of progress in the surgical community; in broad terms, surgeons have accomplished a great deal in reducing death and suffering and have helped define much better approaches to palliative care.

Surgeons have a much better understanding of chronic renal insufficiency and its implications for long-term survival in patients without kidney cancer and extrapolating that information to those with kidney cancer. This understanding has informed new thinking on the benefits of partial versus radical nephrectomy – particularly for patients with small tumors (less than 4 cm.)

Closely related are advances in the development of other tissue-sparing techniques, such as the energy ablative techniques of cryosurgery and radio-frequency ablation.

From a biologic perspective, the surgical community now has a better understanding of the differential risk of various sub-types of the disease and their natural history.

The group also identified the demonstration of the safety and diagnostic accuracy of 18-gauge core needle biopsies as an important development, along with the emergence of systemic therapies – oral medications that are better tolerated by patients than other treatments.

Finally, Group Two noted the convergence of partial nephrectomy, minimally invasive surgery and energy-ablative therapy – which together have significantly enhanced patient outcomes and improved quality of life.

In the face of these advances, though, Group Two noted a number of limitations and areas in which knowledge is still lacking in the surgical community.

For example, in recent years there has been strong support among surgeons for the use of partial nephrectomy as a strategy for patients with small tumors, in order to spare them from long-term health consequences, such as chronic kidney disease. But long-term studies confirming this reasoning are lacking, and a recent randomized trial actually suggested that overall survival may be better for some patients who have radical nephrectomy rather than partial nephrectomy.

Thus, the debate continues about which surgical strategy is better for patients in the long-term. Group Two identified the need for more research on all of the factors related to partial versus radical nephrectomy as a key research priority.

A larger, but related, question is: How can surgeons reliably predict those for whom <u>any</u> kind of treatment will be beneficial? While the kidney cancer community has learned much about the biology of tumors and has refined its treatment options, it could do a better job of determining more accurately who will benefit from surgery and why. For some patients, treatment may be worse than doing nothing.

Group Two felt that part of the reason for this is that the kidney cancer community has focused too greatly on what it knows about tumors and not enough on other factors -- such as co-morbidity and other health risks -- in terms of research focus. The consensus in Group Two was that surgeons need to advance their ability to identify which patients to treat and why.

Group Two also noted a limitation in the surgical community's understanding of the optimal integration of surgery and systemic therapy. What is the potential role of new systemic therapy for patients with larger tumors and existing metastatic disease? Conversely, what is the best role of systemic therapy as an adjuvant for surgical therapy in patients with intermediate disease?

What are the unmet needs for kidney cancer surgical community and what should the priorities of research be over the next 10 years?

Surgeons are focused on early detection, and accordingly, Group Two felt that a major priority of the surgical community should be to develop a better understanding of the prognostic value and true safety of renal-mass biopsy. More study is needed on how to advance percutaneous biopsy in a way that minimizes its complications, such as the risk of tumor dissemination. Better standards for the use of biopsy in guiding therapeutic decisions is also needed, along with better techniques of "risk stratification" in evaluating patients.

Group Two spent significant time discussing the need for more research on active surveillance and how best to manage the many factors that impact surveillance decisions – ranging from tumor size to imaging characteristics and patient quality-of-life. The group also discussed the need for examination of factors to improve decision-making regarding palliative care versus therapy.

Another key area of need is a better understanding of the risk factors for kidney cancer – a research theme emphasized in other discussions during the symposium, as well. The surgical community currently has a poor understanding, from an epidemiological perspective, of risk factors. The group discussed opportunities for early detection, such as developing urine tests, for example, that would indicate the risk for developing neoplasia.

Finally, Group Two identified a need for greater study of the intermediate-risk patient in surgery for metastatic disease. What is the proper role of lymph-node resection or more aggressive surgical resection, for example, in these populations? How do surgeons best incorporate systemic therapy and follow-up while minimizing exposure to radiation and unnecessary testing?

How can the Kidney Cancer Association, industry, the National Cancer Institute and other funding organizations best use their resources to facilitate kidney cancer research?

Group Two felt that the KCA has a strong role to play as an advocate for the development of a more comprehensive, multi-center approach to research. The group noted that the kidney cancer community has not been effective in randomizing trials and that it must think more strategically in order to ensure resources spent in the area of surgical trials is "money well spent." It discussed the inherent difficulties of randomizing studies as a significant hurdle.

At the top of the list for research priorities should be study of needle biopsy, biomarker development and the better collection of tumor data. Group Two discussed the need to create a system – much like that used by the thoracic medical community – in which a core set of data elements is collected from research conducted discipline-wide.

This collaborative, multi-center data collection model could be focused on several key objectives, including study of the role of renal-mass biopsy. A unified process would conceivably yield much more impactful data.

KCA could play an important role in the development of this system – serving as a chief administrative agent and facilitating the creation of a central repository and data-collection activities. Group Two noted that a large-scale effort would be of interest to other strategic partners, such as the National Cancer Institute.

Group Three: Translational Research

What are the most important areas of accomplishment and the major areas of limitation in terms of kidney cancer translational research?

Like Group One and Group Two, Group Three identified the kidney cancer community's new understanding of the VHL gene as one of the most significant research accomplishments over the last decade.

In addition to the other breakthroughs identified in the summaries for Group One and Group Two, Group Three also discussed the Identification of novel secondary gene mutations in histone-modifying enzymes as having a potential impact on future treatment strategies.

Group Three discussed the lack of non-curative molecularly targeted agents (i.e. VEGF-targeted and mTor) as a major weakness in the current treatment environment. With only a handful of agents to work with, treatment breakthroughs are limited.

Additionally, there are no validated patient-selection models, including, as noted in other group discussions, predictive models for cancer recurrence in limited-stage RCC. Also missing are select therapies for advanced RCC.

The group also highlighted the development of resistance to current therapies, the lack of deep understanding and effective strategies for non-clear-cell RCC, and the lack of translational programs as important limiting factors in the current treatment environment. A true multi-disciplinary approach to kidney cancer research is missing.

What are the unmet needs of kidney cancer transitional research and what should the priorities of research be over the next 10 years?

Group Three spent considerable time discussing priorities for research, beginning with the need to develop novel therapies. Resistance to VEGF-targeted therapy is a significant issue that includes delayed resistance (alternate HIF targets and alternate angiogenesis pathways) as well as immediate resistance.

The group agreed that the research community should focus on identifying novel targets; with HIF-2 an emergent driver of kidney cancer, researchers should prioritize strategies to focus on it.

To address the current dearth of patient-selection models, Group Three suggested a new focus on molecular characterization of non-histologic patient specimens. They also noted that more energy should be devoted to advancing the application of novel technologies (NES and micro-RNA, for example), and seeking a better understanding of novel mutation.

Finally, the group discussed intratumoral heterogeneity (metastatic vs. primary) as an important topic for future research attention.

How can the Kidney Cancer Association, industry, the National Cancer Institute and other funding organizations best use their resources to facilitate kidney cancer research?

In terms of resources for the future, Group Three boiled down the need to "patients, tissue and money": That is, a more robust pipeline of clinical trials, a comprehensive system of tissue collection, and increased funding overall.

The group emphasized the need for greater access to human specimens (annotated clinically) and the possible formation of a translational consortium to coalesce efforts.

While Group Three was enthusiastic about the concept of a centralized tumor bank, it recognized the very real challenge of finding funding for it: Where would the substantial capital support needed come from?

In the absence of a tissue repository or a comprehensive tissue collection model, Group Three suggested the development of shared standard operating procedures and clinical annotation for tumor collection. This would help move the research community toward a more integrated and collaborative tissue environment.

Group Three suggested that KCA assume a leadership role in advocating for more research funding, while leveraging industry for access to novel agents. KCA could also play a role in the future as a catalyst to facilitate cross-sector collaboration in research.

Conclusion/Next Steps

"Kidney Cancer Research: Developing a New Vision for the Future" played an important role in bringing together leading researchers for a frank and enlightening discussion of the unique needs of the kidney cancer community.

Participants agreed that it should be considered a first step in a larger effort, which could be moved forward via collaborative partnerships fostered by the Kidney Cancer Association.

Key questions to help anchor those partnerships would center on the feasibility of multi-center, collaborative initiatives and such concepts as a tumor registry or clinical trials consortium.

Broad agreement emerged across all three discussion groups that the kidney cancer research community would benefit from an annotated tumor registry, new structural elements in clinical trials and more robust funding sources for research initiatives.

As a next step, the findings of the symposium will made publicly available at the KCA website and widely shared with stakeholder audiences.

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