Commentary

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Ten Years of Progress in Renal Cell Carcinoma

In the past 10 years, much has changed in the management of advanced renal cell carcinoma (RCC; Figure 1). The treatment of early-stage disease has become less morbid, with the widespread adoption of robotic surgical techniques and the increased utility of thermal ablative techniques. For advanced disease, we have seen FDA approval of 7 new agents.\(^1\)\(^2\) Progress in sequencing technology and copy number analysis has resulted in the discovery of genes\(^5\)\(^9\) and chromosomal regions\(^10\)\(^11\) that may be responsible for disease development or progression. The lives of individuals with RCC are clearly better than they were at the beginning of the last decade. On the other hand, we still have much work to do. Unmet needs are found in the diagnosis and characterization of disease, in the choice of frontline systemic therapy, and in the decisions made at resistance. Much of the information obtained for RCC is focused on clear cell histology, and little is known about optimal treatment for variant histologies. In the next 10 years, we must better match therapy to patients and move from a histologically based to a molecularly based classification of disease.

With identification of the von Hippel-Lindau (VHL) gene\(^12\) and recognition that sporadic mutations of VHL are key drivers of clear cell RCC biology, an entirely new class of agents was developed to block the downstream consequences of hypoxia inducible factor upregulation and resultant vascular endothelial growth factor (VEGF) overproduction. Inhibitors of the VEGF ligand or VEGF receptor entered into clinical trials in the early 2000s. In December 2005, sorafenib became the first agent in this class to be FDA-approved for advanced RCC.\(^6\) A month later, sunitinib was also approved for the same indication.\(^2\) In the next 5 years, bevacizumab plus interferon (IFN) \(\alpha\),\(^7\) pazopanib,\(^8\) and axitinib\(^9\) were also approved.

![Figure 1](advances_in_the_treatment_of_rcc_2002-2012.jpg)

**Figure 1** Advances in the treatment of RCC, 2002–2012. Abbreviations: IFN, interferon; OS, overall survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Although individual studies have, for the most part, not shown a significant intra-study increase in overall survival (OS) for patients treated with antiangiogenic agents as frontline therapy, review of the 40% of patients in the upfront sunitinib versus IFN study who received no subsequent therapy shows a 28- versus 14-month OS, respectively.\(^13\) Additionally, large retrospective reviews of patient outcome after antiangiogenic therapy show a significant upward shift in OS for good- and intermediate-risk patient subgroups when compared with historical data from patients treated with immunotherapy.\(^14\)

In the second-line setting, 2 agents are now FDA-approved. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, showed a 4.9-month progression-free survival versus 1.9-months for placebo in patients who experienced progression on sorafenib, sunitinib, or both.\(^1\) More recently, axitinib, a highly selective VEGF receptor inhibitor, showed a 6.7-month progression-
free survival in a mix of patients who had been treated with immunotherapy or VEGF receptor inhibitor, compared with 4.7 months for patients treated with sorafenib.3

Treatment of individuals with poor-risk features has also advanced in the past 10 years. A randomized phase III study comparing the mTOR inhibitor temsirolimus versus IFN showed a significant prolongation of OS in patients who received upfront temsirolimus.3 Although this improvement is modest, it speaks to an incremental and clinically important advancement in our ability to impact the natural history of advanced RCC, regardless of the initial presenting features.

Patients with advanced RCC clearly have more treatment options today than 10 years ago, and the literature includes statements about the current “embarrassment of riches” in the RCC therapeutic arena. Unfortunately, however, we have not won the battle. Resistance to existing therapies is an almost universal phenomenon, and we do not yet understand the mechanism behind its development. Despite advances in treatment, most patients with advanced disease still face a dramatically shorted life expectancy. An objective look at the therapeutic landscape shows development of only 2 classes of agents after an expenditure of billions of dollars and involvement of thousands of patients in clinical trials, with little to no effort expended on obtaining tissue and blood samples to understand the determinants of response and resistance.

The Next 10 Years
What is the path forward? Academia and industry must work together to develop molecularly based, personalized treatments. The following aims can help focus our attention on key goals.

Define the Best First-Line Therapy
We do not currently have a robust means of identifying individuals most likely to benefit from a particular therapy class or, more precisely, a specific agent. Prognostic algorithms like those based on the Heng criteria and Memorial Sloan-Kettering criteria can be used to predict response and duration of response but are unlinked to any molecular signature or readout. A search for more robust clinical or tissue-based predictors has been underway for some time. Rini et al.16 recently published data showing that development of hypertension while on antiangiogenic therapy and prior history of hypertension were powerful predictors of treatment benefit and OS. Several mechanistic theories exist to explain this observation, but no human tissue–based confirmation exists.

Data from smaller phase II studies17 suggest that specific circulating factors can be used to predict treatment benefit and overall prognosis. The application of massively parallel sequencing technology9 and single nucleotide polymorphism–based copy number analyses10 in RCC allows the molecular characterization of tumors with unprecedented detail and ease. Conducting clinical trials in a way that will provide a robust mechanistic explanation for differential benefit from specific agents and classes of agents will be important. This goal can only be achieved by integrating the analysis of genomic, transcriptomic, and proteomic determinants with the capture of clinical outcomes. This is by nature an iterative process, because initial hypotheses must almost always be refined over time and over serial clinical studies.

Select Appropriate Subsequent Therapy
Duration of disease stabilization can vary considerably among individuals, and mechanisms of resistance may vary. Understanding how resistance develops and which
agent to administer when it presents will require analysis of what changes occur in the
tumor or in the tumor microenvironment as a function of treatment effect. Designing
trials that permit these observations is critical, but the parallel development of tools
that can accurately measure the relevant changes is of equal importance. Because
metastatic disease is not easily accessible in most patients with RCC, performing
biopsies is morbid, expensive, and may be subject to sampling error. A concerted effort
must be made to improve the operating characteristics of biopsy analysis tools and
ensure a thorough understanding of their utility.

With these tools, we must examine the alterations in the tumor epithelial,
endothelial, and stromal compartments as a function of therapy. Trial designs that
permit acquisition of useful material include presurgical and sequential studies. The
former can acquire nephrectomy specimens that have undergone changes as a function
of treatment, and these changes can be linked to clinical outcome. Although the results
are a signature of primary refractoriness, the information can provide valuable insight
into what may be occurring in cases of acquired resistance. Sequential studies can then
be used to evaluate tissue and circulating factors at the time of primary resistance and
assess which second-line agent is efficacious in that specific context.

Discover New Targets

Clearly, the currently available agents cannot eradicate RCC. Despite developing
compounds with picomolar VEGF receptor inhibitory capabilities, we have not
seen an increase in cure fraction beyond a handful of patients. A closer look at the
mechanism of action of currently available agents explains why. Antiangiogenic
agents, by definition, target the tumor endothelium and are not cytocidal against the
epithelial tumor cell. Blockade of TORC1, the key effect of the current generation
of rapamycin-based mTOR inhibitors, is cytostatic. Some preclinical work has been
performed to identify compounds that induce “synthetic lethality” in VHL-deficient
cells. However, more work is needed to identify a potential “Achilles’ heel” in clear
cell and non–clear cell RCC.

An alternate strategy is to rescue the function of mutated protein, thereby altering the
tumor phenotype in RCC cells. Recent work with combined VEGF receptor and MET
inhibitors shows promise as well, and determining which patients will benefit from this
treatment will be important. A renaissance in immunotherapy is occurring. Antibodies
targeting T-cell regulatory receptors are approved for melanoma and are in clinical trials for
RCC. These agents provide hope that harnessing one of the body’s most powerful regulatory
systems may finally be consistently useful to patients with advanced RCC.

Conclusions

A great deal of progress has been made in the treatment of RCC in the past
10 years. We now have treatments that impact tumor biology in a consistent
fashion, and tools are available with which we can measure effect. We must now
use these resources to match treatments to patients and develop novel therapies
and strategies that can actually cure RCC.

References


