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Renal Cell Carcinoma: Molecular Biology and Targeted Therapy

Daniel Su[1], **Lambros Stamatakis**[1], **Eric A. Singer**[2,*], and **Ramaprasad Srinivasan**[1,*]

[1]Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland [2]Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey and Robert Wood Johnson Medical School, New Brunswick, NJ

Abstract

Purpose of review—Renal cell carcinoma (RCC) continues to be the subject of vigorous clinical and translational investigation. Advances in systemic targeted therapies, new molecular pathways, and immunotherapy approaches will be discussed.

Recent findings—Agents targeting the vascular endothelial growth factor (VEGF) and/or the mammalian target of rapamycin (mTOR) pathways continue to be the mainstay for treating metastatic RCC (mRCC). Although enhanced target specificity has improved the toxicity profile associated with newer VEGF-pathway antagonists, durable complete responses remain the exception. Identification of novel pathways/agents, as well as the optimal sequencing and combination of existing targeted agents, remain areas of active study. In addition, emerging data from early clinical trials has reinvigorated interest in immunomodulatory agents.

Summary—The therapeutic armamentarium available to genitourinary oncologists continues to grow but much work remains to be done to fully realize the potential of pathway-specific targeted strategies and immune-based approaches for mRCC.

Keywords

Renal cell carcinoma; targeted therapy; immunotherapy

Introduction

Despite considerable advances in our ability to manage advanced RCC, this disease continues to have a significant public health impact(1, 2). In the United States, RCC is currently the sixth and eighth most common malignancy among men and women, respectively, with 63,920 new cases and 13,860 deaths estimated in 2014(3). The FDA has approved seven targeted agents for the treatment of mRCC(4–11). These agents primarily target i) VEGF, ii) VEGF receptor (VEGFR) with or without additional inhibition of platelet

*Address Correspondence to: Ramaprasad Srinivasan, MD, PhD, Head, Molecular Cancer Section, Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, 10 Center Drive, CRC2-5950, Bethesda, MD 20892, Phone: 301-496-6353, Fax: 301-402-0922, ramasrin@mail.nih.gov; Eric A. Singer, MD, MA, Assistant Professor, Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey, 195 Little Albany Street, New Brunswick, NJ 08903, Phone: 732-235-2043, Fax: 732-235-6596, eric.singer@rutgers.edu.

Conflicts of interest
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derived growth factor receptor (PDGFR), or iii) mTOR(*12). Durable responses to targeted agents are rare and most patients with mRCC eventually progress and die from their disease(13, 14). In contrast, immunotherapy with high-dose interleukin-2 (IL-2) therapy is associated with durable complete responses in <10% of patients. Although curative in a small subgroup of patients, IL-2 treatment is associated with considerable treatment related toxicity and only suitable for carefully selected clear cell RCC (ccRCC) patients(15, 16). Therefore, there is clearly a need for continued evaluation of novel strategies in a bid to improve outcomes associated with this disease.

As we continue to unravel the molecular mechanisms driving kidney cancer, it is important to recognize that RCC is a heterogeneous group of cancers, with disparate genetic and molecular alterations underlying the various recognized histologic subtypes. Future efforts directed at identifying effective targeted strategies against the myriad subtypes of RCC must account for this heterogeneity.

Clear Cell Renal Cell Carcinoma

Most agents available today for the treatment of advanced ccRCC target the von Hippel-Lindau gene (VHL)/hypoxia-inducible factor (HIF)-pathway(17). Recent advances in genomics, epigenetics, and cancer metabolomics have revealed alterations in new pathways that may serve as potential targets for future therapies(**18).

Molecular Biology of ccRCC

Chromatin remodeling refers to the dynamic modification of chromatin architecture, allowing selective access of regulatory factors, such as transcription factors, to the condensed DNA. This is usually carried out by covalent histone modifications (methylation, demethylation, acetylation, and ubiquitination) or ATP-dependent remodeling complexes(*19). Large-scale genetic sequencing of ccRCC tumors has identified a high frequency of mutations in several genes that are involved in the chromatin remodeling process(20–22).

In a study by Varela et al, polybromo 1 (*PBRM1*) was found to be mutated in 41% of ccRCC renal tumors, making it the second most commonly mutated gene in ccRCC, after VHL(22). *PBRM1* encodes the Baf180 subunit of the SWI/SNF chromatin remodeling complex, which plays an important role in regulation of transcription. In a second study, mutations in the genes encoding the SET domain containing 2 (*SETD2*) and BRCA-1 associated protein-1 (*BAP1*) were found in 4% and 8%, respectively, of 98 ccRCC tumors evaluated (21). SETD2 is a histone methyltransferase and BAP1 is a histone deubiquitinase; both are involved in the chromatin remodeling process.

The relationship between mutations in these genes and clinical outcomes is being explored. In one study, targeted sequencing on 185 ccRCC and matched normal tissue confirmed that PBRM1, BAP1, and SETD2 were mutated in 29%, 6%, and 8% of the cases, respectively(*23). In addition, a fourth gene involved with chromatin remodeling, KDM5C, was found to be mutated in 8% of tumors. Tumors with mutations in any one of these genes were more likely to present with stage III disease or higher (P=0.01 and P=0.001,

respectively). BAP1 mutations tend to occur in Fuhrman grade III-IV tumors (P=0.052) and are associated with worse cancer specific survival. Another study evaluating PBRM1 and BAP1 mutations in 145 patients with ccRCC reported that median overall survival (OS) was significantly shorter for patients with BAP1 mutation than for patients with PBRM1 mutation (4.6 vs. 10.6 years, HR 2.7, 95%CI 0.99–7.6, P=0.044); These findings were validated in an independent cohort from The Cancer Genome Atlas (TCGA) study (Median OS 1.9 vs. 5.4 years, for BAP 1 and PBRM1 respectively, HR 2.8, 95%CI 1.4–5.9; P=0.004). Patients with mutations in both PBRM1 and BAP1 had the worst OS in both cohorts (median 2.1 years, 95%CI 0.3–3.8 for study cohort, and 0.2 years, 95%CI 0–1.2 for the TCGA cohort)(*24).

The Cancer Genome Atlas Research Network used a variety of genomic and mRNA platforms and integrative data analyses to provide the most comprehensive molecular characterization of ccRCC to date(**18). In an analysis of primary ccRCC tumors obtained from over 400 nephrectomy specimens, this study confirmed the presence of previously described mutations in VHL and in genes encoding chromatin remodeling proteins. Alterations in components of the PI3K/AKT/mTOR pathway were also identified as a relatively frequent event, a finding that might explain the clinical efficacy of mTOR inhibitors in ccRCC. Another important observation that arose from this study was that more aggressive tumors were characterized by a metabolic phenotype reminiscent of the Warburg effect, with downregulation of the Krebs cycle, accompanied by enhanced fatty acid synthesis and a shift towards increased utilization of the pentose phosphate pathway.

While identification of genetic and epigenetic alterations beyond those affecting VHL activity is a step forward in furthering our understanding of the complex molecular changes underlying ccRCC, it must be emphasized that the precise role of these aberrations remain unclear. It is hoped that these new findings will allow us to better target the key molecular changes underlying ccRCC and lead to the development of prognostic biomarkers.

Evolving Therapeutic Strategies

Current first-line therapies for ccRCC target the VEGF, VEGFR, and mTOR pathways. Optimal combination therapy, strategies for minimizing treatment-related toxicity, sequencing of available therapies, and emerging immune based therapies continue to be explored in an effort to improve the clinical outcome in patients with advanced ccRCC.

First-Line Agents

Two recent trials evaluated the comparative efficacy and tolerability of sunitinib and pazopanib. The COMPARZ trial was a prospective, randomized, non-inferiority study of pazopanib versus sunitinib in 1,100 previously untreated patients that compared efficacy, toxicity, and quality of life measures(*25). Median PFS was 8.4 months and 9.5 months, respectively for pazopanib and sunitinib (HR 1.05, 95%CI; 0.90–1.22). Likewise, there were no significant differences in response rates and OS between the two agents. However, health-related QOL measures were superior in the pazopanib group, with less fatigue and fewer/less severe symptoms associated with the hand-foot syndrome than in the sunitinib group. In contrast, there was a higher discontinuation rate in the pazopanib group (24%)

compared to the sunitinib group (20%), which was primarily due to a significantly higher rate of liver function abnormalities.

The PISCES trial further attempted to identify tolerability differences between these 2 agents(26). 168 previously untreated patients with mRCC were randomized to receive pazopanib for 10 weeks followed by a 2-week washout and then sunitinib for 10 weeks (4 week on /2 week off schedule) or vice versa. At 22 weeks, the patients completed a questionnaire assessing preference of agents. Pazopanib was preferred by 70% of the patients, while sunitinib was preferred by 22% of the patients (8% had no preference between the agents). This data strengthens the rationale of using either of these agents as first-line therapy for patients with metastatic ccRCC. Although pazopanib may be better tolerated overall, there is a subset of patients that will do better with sunitinib; crossover should be considered if tolerability becomes an issue.

Sequencing of Targeted Therapies

Standard treatment paradigms often involve the initiation of an mTOR inhibitor after disease progression on a VEGF TKI. This is supported by the RECORD-1 study which showed a longer progression free survival (PFS) in patients treated with everolimus compared with placebo after failure of front-line VEGF therapy(27). The RECORD-3 (NCT00903175) study addressed the issue of whether the sequence in which VEGF and mTOR agents were administered might impact outcome(28). 471 patients with untreated mRCC (any risk category, 85.4% had clear-cell histology) were randomized to receive either first-line sunitinib or everolimus until disease progression, at which point they crossed over to the alternate drug. The primary endpoint was to assess non-inferior PFS of first-line everolimus compared to first-line sunitinib. Median PFS was 7.9 months (95%CI:5.6–8.2months) and 10.7 months (95%CI:8.2–11.5months) for the everolimus group and sunitinib group, respectively; this was found to be statistically significant (HR 1.43, range 1.15–1.77). At the time of the analysis, median OS was 22.4 vs. 32.0 months in the everolimus and sunitinib groups, respectively (HR 1.24, 95%CI:0.94–1.64), trending towards worse OS in the everolimus group. While the results are still preliminary, it appears that the standard sequence (TKI first, then mTOR agent) used commonly in clinical practice, particularly in patients with standard-risk disease, results in better outcomes than using an mTOR agent first.

Combining Targeted Therapies

Due to the unique target profile of each individual agent, it has been proposed that combinations of a VEGF and an mTOR agent could be synergistic. Although combinations of first generation multi-tyrosine kinase inhibitors such as sunitinib with mTOR inhibitors are associated with unacceptable toxicity(29, 30), the adverse event (AE) profile associated with selective VEGF targeted agents has allowed successful combination strategies using agents such as bevacizumab.

The INTORACT trial compared the combination of temsirolimus plus bevacizumab to bevacizumab plus interferon-α (*31). 791 patients with previously untreated metastatic ccRCC were randomized to one of the aforementioned groups; the primary endpoint was

PFS. There was no significant difference between the bevacizumab/temsirolimus and bevacizumab/interferon-α groups in median PFS (9.1months vs. 9.3months, HR 1.1; 95%CI: 0.9–1.3; P=0.80), OS (25.8months vs. 25.5months, HR 1.0; 95%CI:0.9 to 1.3; P=0.6) or objective response rates (27.0% vs. 27.4%, RR 1.0; 95%CI:0.8–1.3; P=1.0). The combination of temsirolimus plus bevacizumab, however, appeared to be better tolerated, with superior symptom scores, as assessed by validated symptom indices. A second study (RECORD-2) also demonstrated that addition of an mTOR inhibitor (everolimus) rather than IFN-α to bevacizumab did not provide significant clinical benefit(32).

Investigational Targeted Therapies

Several newer targeted agents have been studied in mRCC. Tivozanib is a selective inhibitor of VEGFR 1–3 and initially showed promise in the mRCC population with fewer AE than other TKIs by historical comparison (33). The results of the TIVO-1 trial comparing tivozanib with sorafenib in previously untreated mRCC patients were published(*34). The primary endpoint was PFS and secondary endpoints included OS and safety/tolerability. While there was a significantly longer median PFS in the tivozanib arm (11.9 vs. 9.1months; HR 0.80; 95%CI:0.64–0.99; P=0.042), there was a trend towards better median OS in the sorafenib arm (28.8 vs. 29.3months; HR 1.25; 95%CI:0.95–1.62; P=0.11). Based on these data, the FDA rejected tivozanib for use in the mRCC population.

Fibroblast growth factor receptor (FGFR) 1 has been proposed as a possible therapeutic target in patients with advanced RCC(35, 36). Dovitinib, an inhibitor of VEGFR, PDGFR, and FGFR was studied in an open-label randomized phase III trial (NCT01223027) in patients with metastatic ccRCC who had received 1 prior VEGF and 1 prior mTOR therapy (37). 570 patients were randomized to dovitinib or sorafenib with PFS as the primary endpoint. Most patients had received an anti-VEGF agent (92%) followed by an mTOR agent before enrollment. PFS was comparable, with a median of 3.7 and 3.6 months (HR 0.86, 95%CI:0.72–1.94, P=0.063) in the dovitinib and sorafenib arms, respectively. Median OS was similar at 11.1 (dovitinib) and 11 months (sorafenib) (HR 0.96; 95%CI:0.75–1.22; P=0.357). A second study (NCT01024920) with nintedanib (anti-FGFR) suggested that this agent was similar in efficacy to sunitinib in patients with untreated ccRCC(38). While the two aforementioned studies dampen enthusiasm for further evaluation of FGFR1 inhibitors in RCC, it must be noted that there was no attempt made in these studies to select patients based on evidence of FGFR1 pathway activation in their tumors. Additionally, there were no pharmacodynamic endpoints reported, rendering it impossible to determine if effective FGFR1 inhibition was achieved with either of these drugs.

Immune Based Strategies

Immune Checkpoint Inhibitors

Checkpoint receptors (CPR) on immune effector cells such as CD8+ T lymphocytes function by blocking co-stimulatory signals at specific stages of immune activation upon ligand binding, which results in peripheral tolerance and immunosuppression. Agents that block these CPR can therefore improve the patient’s ability to mount an effective antitumor immune response. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) is a CPR

expressed by T-cells. Earlier studies have reported activity of ipilimumab, a CTLA4 monoclonal antibody, in RCC; Yang et al showed durable responses in patients treated with this agent, including responses in patients who did not previously respond to IL-2(39).

Programmed Cell Death 1 (PD-1) receptor is a T-cell receptor, whose ligands (PD-L1, PD-L2) are expressed on the surface of tumor cells. Patients whose tumors contain PD-1 positive tumor infiltrating lymphocytes (TIL) are more likely to have larger tumors, higher grade tumors, advance stage RCC, and sarcomatoid differentiation than patients without PD-1 positive TIL(40). Engagement of PD-1 on T-cells by its ligand leads to downregulation of antigen-driven immune responses(41). Both PD-1 and its primary ligand, PD-L1, have been explored as potential therapeutic targets in ccRCC.

In a phase 1 study, patients with advanced solid tumors were treated with nivolumab (anti-PD-1 antibody)(**42). A total of 33 RCC patients were enrolled, and 9 patients (27%) had an objective response. Encouragingly, of 8 patients on treatment for 1 year or more, 5 had a sustained response. Stable disease lasting ≥24 weeks was seen in an additional 9 patients (27%). Interestingly, pretreatment tumor specimens from 42 patients (5 RCC) were analyzed for PD-L1 expression on the surface of tumor cells. None of the 17 patients with PD-L1 negative tumors experienced a response while 9/25 (36%) with PD-L1 expression had an objective response, suggesting that PD-L1 expression should be further evaluated as a predictive biomarker.

A phase I dose escalating trial with BMS-936559, a PD-L1 specific monoclonal antibody, was conducted in patients with advanced solid tumors(**43). Out of 75 patients, 17 had RCC. Two out of 17 patients (12%) had an objective response, with duration of response of 4 and 17 months. Seven additional patients (41%) had stable disease lasting at least 24 weeks.

Several ongoing clinical trial are further evaluating the efficacy of PD-1 checkpoint inhibitors in mRCC, including a phase III comparative study of nivolumab versus everolimus in mRCC patients who were pretreated with antiangiogenic therapy (NCT01668784).

Non-clear Cell Renal Cell Carcinoma

The only available category 1 recommendation for systemic treatment of non-clear cell RCC (nccRCC) is the use of temsirolimus in patients with poor-risk features(5, 44). Although targeted agents directed against the VEGF and mTOR pathways are frequently used to treat nccRCC, outcomes are inferior to those seen in patients with ccRCC(2, *45).

Molecular Biology of Papillary RCC

Although the key molecular alterations underlying the majority of papillary renal cancer (pRCC) are still unknown, accumulating data suggest a role for at least two well defined pathways in certain subtypes. Type 1 pRCC, particularly those associated with the hereditary form of this cancer (HPRC), demonstrate activation of the HGF/MET pathway(46). Patients with HPRC have germline activating mutations in MET, which render

this proto-oncogene constitutionally active. The role of this pathway in sporadic forms of pRCC remains under investigation, but somatic mutations of MET, as well as duplication of the chromosome bearing both MET and its ligand HGF(chromosome 7), have been seen in these tumors.

A second form of hereditary pRCC is associated with alterations in the fumarate hydratase gene (*FH*), which encodes a TCA cycle enzyme that catalyzes the conversion of fumarate to malate. Germline *FH* mutations are seen in patients with hereditary leiomyomatosis and renal cell cancer (HLRCC), a condition associated with a highly aggressive variant of type II pRCC(17). Loss of FH activity promotes a metabolic shift in these tumors, characterized by disruption of the Krebs cycle and a consequent reliance on aerobic glycolysis to satisfy cellular bioenergetic requirements.

It has long been recognized that accumulation of fumarate, resulting from FH inactivation, leads to a VHL-independent upregulation of intracellular HIF, and transcriptional activation of downstream proangiogenic and growth factors. More recently, it has been demonstrated that intracellular fumarate accumulation is associated with an oxidative stress response signature characterized by upregulation of the Nuclear factor [erythroid-derived 2]-like 2 (NRF2) pathway. The activity of NRF2 is largely regulated by association with Kelch-like erythroid-derived Cap-n-Collar Homology (ECH)-associated protein 1 (KEAP1) and Cullin 3 (CUL3), subunits of the E3 ligase complex that bind to and target NRF2 for ubiquitin-mediated degradation(47). In FH deficient cells, accumulation of fumarate leads to a post-translational modification of cysteine residues (succination) in several proteins, including KEAP1. Succination of KEAP1 leads to impaired NRF2 binding and consequent upregulation of this molecule.

Although NRF2 activation is also seen in sporadic forms of type II pRCC, somatic mutation of FH does not appear to be a common event(48). Instead, a recent study suggests that somatic mutations in NRF2 and CUL3 may be responsible for the NRF activation phenotype(*49). Further elucidation of the role of the KEAP1-CUL3-NRF2 pathway might provide insights into the pathogenesis of pRCC and create new opportunities for therapeutic intervention.

Therapeutic Strategies in non-Clear Cell RCC

The interim results of a phase II study of bevacizumab plus erlotinib (NCT01130519) in patients with metastatic pRCC were recently presented(50). This phase II study included 34 subjects, of whom 20 had sporadic pRCC and 14 had known HLRCC. Most subjects were Memorial Sloan-Kettering Cancer Center intermediate risk category (24/34, 70%), and 16 subjects had received at least one prior systemic therapy. The overall RECIST response rate was 32% (11/34) in the entire cohort with a disease control rate (partial response plus stable disease) of 65%. Partial responses were seen in 6/14 (43%) subjects with HLRCC and 5/20 (25%) subjects with sporadic pRCC. After a median follow up of 10.7 months, median PFS was 10.5 months (95%CI:7.4–18.6months). While the initial results are promising, further follow-up will help determine the efficacy of this regimen in the pRCC population.

RAPTOR (NCT00688753) is an open-labeled, multicenter phase II clinical trial evaluating everolimus as first-line agent in patients with metastatic pRCC. Results from this trial were recently reported in abstract form. At the time of a preliminary intent-to-treat analysis (n=83), median PFS was 3.7 months (95%CI:2.4–5.5), while median OS was 21 months (95%CI: 15.4–28). Common grade ≥ 3 AEs included asthenia (10.6%), fatigue (5.4%), and anemia (5.4%). 27.2% of the patients discontinued treatment due to AEs(51).

A second phase II trial of everolimus in patients with metastatic nccRCC was recently published(52). Of the 49 patients enrolled, 29(59%) had pRCC. Twenty three patients (47%) had prior anti-VEGF therapy. Partial response was noted in 5(10%), stable disease in 25(51%), and disease progression in 16(32.7%) patients, respectively. Interestingly, 2 out of 5 patients with objective response to everolimus had chromophobe RCC, whereas 2 had pRCC and 1 had an unclassified RCC variant. The median PFS in this study was 5.2 months, and patients with chromophobe RCC had a trend towards longer PFS compared to other nccRCC patients (P=0.084).

Based on the two foregoing trials, everolimus appears to have modest activity in patients with pRCC/nccRCC, and effective standard of care options remain elusive for these patients.

Conclusion

Targeted therapies directed against VEGF, VEGFR, and mTOR continue to play a crucial role in the management of metastatic ccRCC, although the optimal first-line agent for non-clear cell histologies is much less defined. Selective VEGFR inhibitors might be better tolerated compared to first generation agents such as sunitinib, without significant differences in clinical activity. Unfortunately, attempts to optimize outcomes through alternative sequencing of available agents or combination strategies have been largely disappointing. Immune modulation via immune checkpoint inhibitors appears very promising in early clinical trials and likely to further our efforts to combat ccRCC. With better understanding of the molecular diversity underlying the many distinct subtypes of nccRCC, it is hoped that more effective, personalized mechanism-based therapeutic strategies can be developed against these entities.

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Key points

- Targeted agents against VEGF, VEGFR, mTOR continue to play a crucial role in the management of metastatic ccRCC
- Combination therapy and alternative sequencing of agents have been largely disappointing, with little positive impact on clinical benefit
- Novel immunomodulatory agents offer early promise and are under investigation in phase 3 trials
- Genomic studies offer new insights and may help identify potential targets for the treatment of both ccRCC and nccRCC